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VACCINATION WITH AVIANIZED SMALLPOX VACCINE

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VACCINIA virus for Jennerian prophylaxis is still prepared in calves despite the fact that material obtained in tissue cultures or embryonated eggs has been employed for the past twenty years. The most important types of culture virus which have been used are (1) the tissue-culture virus of Rivers and Ward [1-3] and (2) the vaccine virus grown on the chorioallantoic membrane of the developing chick embryo by Goodpasture, Buddingh, and co-workers.[4-7] The continued cultivation of vaccinia virus in a medium consisting of minced chick embryo tissue and Tyrode's solution has resulted in a virus qualitatively changed to such an extent that considerable amounts of it could be injected intradermally into human beings without danger or inconvenience. Recently Cabasso and associates[8] have shown that chick embryo vaccine is antigenically equal to and, to a great extent, simpler to prepare than calf lymph vaccine. In a comparative study in which smallpox vaccine preparations of either calf lymph or chick embryo origin, glycerinated or vacuum dried, were used no qualitative or quantitative difference were observed between the primary takes. The field use of chick membrane smallpox vaccine in Texas has also been reported.[9] Over two million vaccine doses have been prepared and distributed in that state with 88 per cent primary takes in previously nonvaccinated persons under field conditions, whereas 100 per cent primary takes were obtained under controlled experimental conditions. In addition, there was some evidence that the chick embryo type vaccine was successful in controlling an outbreak of smallpox in Texas.[10]

The question of preparing a smallpox vaccine of better stability than glycerinated calf lymph vaccine has occupied a number of investigators. Cardone[11] was able to reduce highly contaminated smallpox calf lymph in bacterial count until it became acceptable for the production of vaccines to be used for human vaccination by grinding the lymph in calf globulin and adding phenol and ether to the emulsion. When this product was dehydrated it suffered little loss of potency. After storage of the vaccine for more than a year at 20° to

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25° C. or for thirty to forty days at 37.5° C. the vaccines were still potent enough to warrant their use for human vaccination.

The present article is a report on some observations in children vaccinated with chick embryo-type vaccine.* Three types were employed: glycerinated chick embryo vaccine; sorbitole-stabilized fluid vaccine; and vacuum-dried (lyophilized), sorbitol-stabilized vaccine.

The method of preparing glycerinated smallpox vaccine of chick embryo origin has been described in detail by Cabasso and associates.[8] The sorbitol-stabilized fluid vaccine was prepared in a manner identical to that for glycerinated vaccine, except that glycerine was substituted by sorbitol. The vacuum-dried (lyophilized), sorbitol-stabilized vaccine was prepared by the method described by Cabasso and co-workers,[8] 5 to 7 per cent sorbitol being added to the virus suspension prior to lyophilization. This particular lot had remained at room temperature for several months before being used by us. The smallpox vaccine was shipped in dry ice and kept in the refrigerator until ready for use. A vial consisted of lyophilized material which was reconstituted with 2 ml. of the diluent which was also provided together with the vacuum-dried material. The diluent was added and the mixture allowed to stand for several minutes. Thereafter, rather vigorous shaking was necessary to reconstitute the material into a homogenous tissue suspension. About twenty-five to thirty children were vaccinated at the same time in order to facilitate observations. The type of reaction and the progression of the reaction were observed and compared with vaccination made with recently prepared fluid vaccine.

The site of the vaccination was the outer side of the upper arm on the skin approximately over the insertion of the deltoid muscle. A volatile antiseptic was used to clean the skin. The multiple pressure method was used almost exclusively. A series of from eight to ten downward pressures was employed. Dressings were not used.

The primary reaction as observed corresponded closely to that seen following vaccination with standard calf lymph virus vaccine. A red papule was noticed after from three to six days. This was followed by a small vesicle which enlarged and reached its maximum diameter at about the eighth day. The usual erythematous area with slight induration was also noted. This was followed by a dark crust which remained for about one week or more (Fig. 1, *A*, *B*, and *C*).

The so-called "accelerated" or "vaccinoid" reaction corresponded to the description generally used.[12] One or two types of local reactions were encountered: the one starting on about the third day began as a papule and progressed to the formation of a vesicle which reached its maximum and crusted before the seventh day. "The third type of local reaction commonly seen after revaccination is less definite and difficult, if not impossible, to interpret with confidence. Beginning within twenty-four hours as a small itchy papule this reaction has reached a maximum by the third day and, although it commonly develops a

*This avianized vaccine was supplied to us through the courtesy of Dr. J. Ruegsegger of Lederle Laboratories.

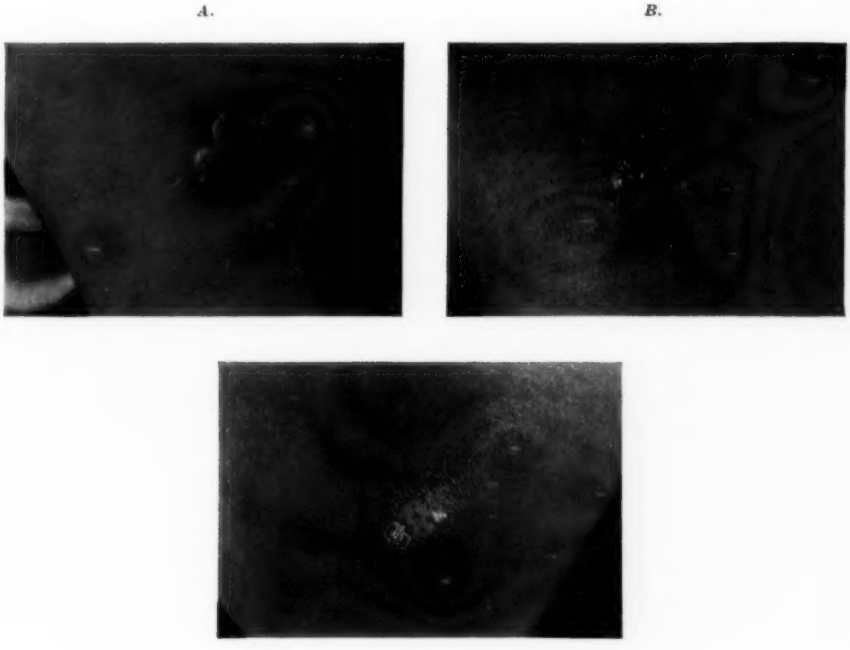

Fig. 1.—Vaccination reaction following vaccination with avianized smallpox vaccine. *A*, 1 week; *B*, 2½ weeks; *C*, 4 weeks.

small head which eventually desquamates, it does not usually form a true vesicle, and only rarely one which extends in size beyond the small area over which the needle pressure or scratch was made. After the third day this form of reaction generally disappears rapidly, but in some persons it may persist and still irritate, but without further increase in size, for a week or ten days." This type of reaction is referred to as "immune" reaction.

More than 400 children were observed in this study. They were divided into three groups: (a) those receiving glycerinated chick embryo vaccine—285 cases; (b) those receiving the sorbitol-stabilized fluid chick embryo vaccine—44 cases; and (c) those receiving the vacuum-dried, sorbitol-stabilized chick embryo vaccine—85 cases. The children ranged in age from 6 months to 12 years and comprised infants vaccinated either in clinics or in private practice and children with inactive tuberculous infection observed in the children's ward of Sea View Hospital. The results are summarized in Tables I to III.

TABLE I. RESULTS OF VACCINATION OF CHILDREN WITH GLYCERINATED CHICK EMBRYO VACCINE

AGE	NO.	RESPONSE		
		PRIMARY TAKE	ACCELERATED REACTION	IMMUNE REACTION
Under 6 mo.	12	10		
6 mo. to 1 yr.	95	86		
More than 1 yr.	178	152	14	12
Total	285	248		

There were 285 children vaccinated with glycerinated chick embryo vaccine (Table I). They ranged in age from 3 to 22 months. The majority of children were in the age group of 6 to 12 months. Of these, 274 showed a positive take, including 248 primary takes. The vesicles ranged in size from ⅛ to ¾ inch, and the erythematous area from 1 to 2 inches. Occasionally, marked induration was noted. The temperature rarely lasted for more than two days, the height usually being reached on the eighth day. A number of children showed no rise in temperature at all. The highest temperature observed was 105° F., lasting for twenty-four hours in one child. Axillary adenitis of moderate extent was also seen. The size of the vesicle and of the erythematous area corresponded closely to those seen following vaccination with glycerinated calf lymph virus vaccine.

TABLE II. RESULTS OF VACCINATION OF CHILDREN WITH SORBITOL-STABILIZED FLUID CHICK EMBRYO VACCINE

AGE	NO.	RESPONSE		
		PRIMARY TAKE	ACCELERATED REACTION	IMMUNE REACTION
6 to 12 mo.	35	34		
Over 1 yr.	9	8		

TABLE III. RESULTS OF VACCINATION OF CHILDREN WITH LYOPHILIZED, SORBITOL-STABILIZED CHICK EMBRYO VACCINE

AGE	NO.	RESPONSE		
		PRIMARY TAKE	ACCELERATED REACTION	IMMUNE REACTION
6 to 12 mo.	8	8		
Over 1 yr.	77	34	22	21

There were forty-four children who received sorbitol-stabilized fluid chick embryo vaccine (Table II). Of these, two had a negative reaction and the remainder showed a positive test indistinguishable from the reaction described above following vaccination with glycerinated calf lymph virus vaccine.

Eighty-five children were vaccinated with sorbitol-stabilized, vacuum-dried chick embryo vaccine (Table III). They were patients of the children's service of Sea View Hospital. Vaccinations were performed in three sessions. Forty-two children, ranging in age from 6 months to 10 years, had no history of previous vaccinations. Of these, all showed a primary take. Of the forty-three children with a history of previous vaccination, twenty-two presented "accelerated" reaction to the vaccination and twenty-one children showed an "immune" reaction, as described above. These children ranged in age from 12 months to 12 years. Side reactions to the vaccination with sorbitol-stabilized fluid chick embryo vaccine, as well as reactions with lyophilized vacuum-dried chick embryo vaccine, were mild in general; temperature rarely exceeded 101° F., and many children showed no febrile reaction at all. Since the children were carefully observed on the ward of a hospital, detailed observations of their temperature charts could be obtained. No undue reactions to egg protein[13] were encountered in children observed in this study.

COMMENT

It appears from these investigations that vaccinia virus as prepared in the chick embryo may be safely used for smallpox vaccination. The vaccine as employed in our tests appears to possess qualities similar to a potent calf lymph virus vaccine. Side reactions were mild and no complications ensued. In many instances there was a complete absence of fever. The local reactions, as observed, compared favorably with those seen following vaccination with calf lymph vaccine. The results do not indicate the degree and length of immunity following vaccination with chick embryo material. This question will be studied in further tests. In the laboratory tests, however, the preparations meet the requirements of standard potency titrations as prescribed by the National Institute of Health. Ruegsegger,[14] using chick embryo vaccine in a large group of children in Puerto Rico, found immune reactions in a considerable percentage on revaccination with potent calf lymph vaccine after one year. The results with the sorbitol-stabilized material were particularly gratifying, since the results of positive takes were nearly 100 per cent in those with a negative history of previous vaccination.

Vaccinia virus prepared on the chorioallantois of the developing chick embryo has many advantages. It can be produced in large quantities within a relatively shorter period of time than calf lymph virus vaccine. The experience in New York City (1947) with attempted large-scale vaccination of millions of people has shown the difficulty involved in obtaining sufficient vaccine in times of need. The fact that vaccinia virus derived from chick embryo may be stored in a lyophilized form for long periods of time and still retain its potency provides an additional factor for recommending its use. The material is bacteriologically sterile and no microorganisms are introduced when it is used for vaccination.

There is a natural opposition to changing a procedure which has been employed for over a hundred years and produced satisfactory results.

The present study confirms observations made by a number of investigators that the chick embryo method can be safely utilized for smallpox vaccination.

SUMMARY

Four hundred fourteen children, ranging in age from 3 months to 12 years, have been vaccinated with smallpox vaccine of chick embryo origin. Fluid, as well as reconstituted vacuum-dried, vaccines have been employed. The results were satisfactory, with a large percentage of susceptible children showing primary takes. Side reactions were mild and no complications ensued. The advantages of employing vaccinia virus material prepared on the chorioallantoic membrane of the developing chick embryo are discussed.

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SPONTANEOUS PNEUMOTHORAX IN THE FIRST TEN DAYS OF LIFE

With Review of the Literature

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PNEUMOTHORAX in the newborn infant has been clinically recognized by many observers since Ruge's[1] initial report in 1878 in which he reported a tension pneumothorax found at post mortem in an infant born after a difficult breech extraction. Since the advent of roentgenologic diagnosis, scattered reports[2-37] describing pneumothorax in the neonatal period have appeared. Silver[28] suggests that the descriptive term spontaneous pneumothorax in the newborn be limited to pneumothorax occurring during the first five days of life, excluding those secondary to infection. Silver postulates that such cases are secondary to obstructive emphysema during the time respiration is being established in the immediate post-natal period.

DEFINITIONS

Spontaneous pneumothorax is used in this paper to indicate the presence of gas in the pleural space as demonstrated by roentgenogram or autopsy without obvious cause such as infection or surgery. *Mantle* pneumothorax is a small partial pneumothorax in which the roentgenogram shows the lateral border of the lung roughly parallel to the thoracic wall. *Alternating* pneumothorax is the appearance of gas first in one pleural space and later in the other. *Bilateral* pneumothorax is the simultaneous appearance of gas in both pleural spaces. *Tension* pneumothorax is more difficult to define precisely. For cases reviewed and tabulated we relied entirely upon the written statement of the previous author and had to assume that, if tension pneumothorax was not mentioned specifically, it was not present. For the patients herein reported tension pneumothorax is subdivided into *proved* and *suspected* cases. The former is defined as pneumothorax which demonstrated contralateral shift of the mediastinum, widening of the homolateral intercostal spaces, and depression of the homolateral diaphragm by roentgenogram, and release of gas under pressure upon thoracentesis. Suspected tension pneumothorax describes cases which exhibited the roentgenographic picture described above in lesser degree and in which thoracentesis was not done. This paper will only review previously reported cases of alternating, bilateral, and tension spontaneous pneumothorax in the first ten days of life. Nine new cases of spontaneous pneumothorax in the first ten days of life will be presented.

INCIDENCE

The reported incidence of pneumothorax in the newborn varies from

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0.07 per cent[13] to 37.5 per cent.[33] Davis and Stephens[7] in 1930 detected six cases among 702 consecutive newborn infants by routine chest films and their 1 per cent figure is widely quoted in standard pediatric textbooks as the actual incidence. Solis-Cohen and Bruck[30] in 1934 reported a line suggesting pneumothorax in eleven out of 500 infants. Wieland[33] in 1937 reported pneumothorax in fifteen out of forty (37.5 per cent) premature infants seen in his clinic over a seven-month period and ten more cases of pneumothorax out of an unspecified number of term infants seen in the same period. Harris and Steinberg[13] in 1954 detected six cases during the first 6 days of life in 8,716 (0.07 per cent) live-born infants by physical examination and chest films where indicated. It is unlikely that the actual incidence of pneumothorax in the newborn could vary as widely as the figures quoted above would indicate. This wide variation can be explained by thoughtful consideration of the time, technology, and geography involved.

All of the reports giving the higher incidences of pneumothorax occurred from 1930 to 1937. Davis and Stephens[7] used $\frac{1}{10}$ second, 30 MA, 60 KV, at 30 inches, a technique today considered unsatisfactory for newborn chest films. Although the standard technique for Solis-Cohen and Bruck,[30] Wieland,[33] Bertin,[4] Hotz,[15, 16] Holz,[14] and Riedweg[22] was not recorded in their papers, it was probably similar to that used by Davis and Stephens[7] in 1930. Solis-Cohen and Bruck[30] would not conclusively say that their cases represented pneumothorax, and the lines suggesting pneumothorax were not found on both inspiratory and expiratory films. Both Wieland[33] and one of the discussants of his paper questioned the interpretation of his films which gave him such an extremely high incidence of pneumothorax in premature infants (37.5 per cent) and it was suggested that the lines might be due to motion of the patients. Skin lines, motion of the newborn patient, and other artifacts present problems today as they must have to the authors mentioned above. Out of the approximately 150 cases[1-37] of pneumothorax in the newborn reported or mentioned in English medical literature, forty-three were reported by four Swiss authors (Holz[14] and Wieland[33] of Basel, and Hotz[15, 16] and Riedweg[22] of Zurich) between 1934 and 1937. All of the cases reported by these authors had partial or mantle pneumothorax, conservative treatment without aspiration, no confirmation of pneumothorax by thoracentesis or autopsy, and little correlation of clinical condition and roentgenographic findings. All infants survived except one who was found to have transposition of the great vessels at post mortem.

We agree with Biering[5] who suggested that some cases reported as pneumothorax in reality may have been pseudopneumothorax. The incidence of pneumothorax of the newborn today is probably close to the 0.07 per cent reported by Harris and Steinberg[13] in 1954.

ALTERNATING, BILATERAL, AND TENSION PNEUMOTHORAX

The five cases of alternating pneumothorax in the newborn reported in the literature have been tabulated in Table I. For the reasons mentioned earlier, we feel that the cases reported

TABLE I. ALTERNATING PNEUMOTHORAX IN THE FIRST TEN DAYS OF LIFE

AUTHOR DATE	WEIGHT (GRAMS)	SEX	CONDITION AT BIRTH	ONSET OF SYMPTOMS	DIAGNOSIS OF INITIAL SIDE AND TYPE	DIAGNOSIS OF ALTERNATE SIDE AND TYPE	TREATMENT	TERMINATION	REMARKS
Hotz[15] 1934	3,010	F	Good	5 days	9 da. Right mantle	12 da. Left mantle	Conservative	Survived	Normal chest at 22 da.
Riedweg[22] 1934	2,720	F	Apneic, cyanotic, stridor	Birth	1 da. Right, partial	36 da. Left mantle	Conservative	Survived	Normal chest at 50 da.
Holz[14] 1936	3,060	F	Asphyxia, aspirated blood and mucus, resuscitated	Birth	4 da. Left mantle	7 da. Right, small partial	Conservative	Survived	Seizures, normal chest at 12 da.
Singleton[29] 1940	8 mo. gestation	?	Hard labor, difficult resuscitation, cyanotic	Birth	1 da. Side not stated	4-5 da. later, Opposite side	Conservative	Survived	Normal chest at 14 da.
France et al.[11] 1952	2,965	F	Fetal distress, forceps, asphyxia	Birth	63 hr. Left, no tension	73 hr. Right, partial	Aspiration Antibiotics	Survived	Normal chest at 9 da.

Note: Conservative treatment means oxygen and stimulants.

TABLE II. BILATERAL PNEUMOTHORAX WITHOUT TENSION IN THE FIRST TEN DAYS OF LIFE

AUTHOR DATE	WEIGHT (GRAMS)	SEX	CONDITION AT BIRTH	ONSET OF SYMPTOMS	DIAGNOSIS AND TYPE	TREATMENT	TERMINATION	REMARKS
Miller[21] 1926	?	?	Forceps, moderate asphyxia	5 da.	5 da., bilateral	Conservative	Died at 12 da.	Cystic lung on post mortem
Holz[14] 1936	2,100	?	Cyanotic, dyspneic	Birth	2 da., bilateral mantle pneumothorax	Conservative	Survived	Malformed chest, prominent xiphoid
Rothman[25] 1937	3,870	M	Cesarean, labored respiration, moderate cyanosis	Birth	25 hr., small right, large left pneumothorax	Conservative	Survived	Normal chest physical examination at 3 da. Normal chest film on 4th da.
Biering[5] 1941	2,400	M	Feeble cry, cyanotic, gasping respirations	Birth	12 hr., right mantle pneumothorax, small left pneumothorax	Conservative	Survived	Normal chest film at 4 wk.
Elkin[10] 1941	3,690	F	Low forceps, asphyxia	Birth	Autopsy, bilateral pneumothorax	Conservative (artificial respiration)	Died at 22 min.	Autopsy showed atelectasis, fractured clavicle, subtentorial hemorrhage, subpleural emphysematous blebs, postperitoneal emphysema
Salmon and Forbes[26] 1943	3,270	F	Cyanotic, labored respirations, cord around neck	Birth	7 hr., bilateral with shift of mediastinum to right	Conservative	Survived	Spina bifida occulta; 4 da., small left pneumothorax; subsequent films normal
Salmon et al.[27] 1947	2,700	M	Good	12 hr., cyanotic respiratory distress	20 hr., bilateral with shift of mediastinum to right	Aspiration of left, O_2 and CO_2	Died at 24 hr.	Pulmonary subpleural blebs, interstitial emphysema on post mortem
Strain and Connell[32] 1950	2,325	F	Cesarean, good	4 da. lethargic, mildly cyanotic	5 da., bilateral mantle pneumothorax	Conservative	Survived	Mantle pneumothorax on 6th da.; normal on 9th da.
Harris[36] 1955	3,060	M	Spontaneous cry, good color	Shortly after birth, cyanosis; rapid shallow respirations	Less than 4 hr., bilateral with mediastinal emphysema	Oxygen, bilateral aspiration	Died at 4 hr.	Older sibling died shortly after birth with same condition one year previously; post-mortem examination on both infants revealed no cause for pneumothorax

TABLE III. TENSION PNEUMOTHORAX IN THE FIRST TEN DAYS OF LIFE

AUTHOR DATE	WEIGHT (GRAMS)	SEX	DELIVERY	CONDITION AT BIRTH	ONSET OF SYMPTOMS	DIAGNOSIS AND TYPE	TREATMENT	TERMINATION	REMARKS (POST MORTEM)
Ruge[1] 1878	4,412	F	Difficult breech	Asphyxiated	Birth	Post-mortem left tension	Conservative	Died at 24 hr.	Rupture of an emphysematous vesicle; 3 cm. tear found in pleura
Diessler[9] 1933	Term	M	Difficult labor, low forceps	Cyanotic	Birth	Post-mortem, bilateral	Conservative; Drinker respirator	Died first day	Marked emphysema, hydronephrosis, cystic kidneys, bilateral hydroureter
Wood and Paine[34] 1941	3,450	M	Spontaneous	Cyanotic, soon breathed well	Birth	31 hr., right tension pneumothorax	Aspiration and underwater trap	Died at 39 hr.	Emphysematous blebs over both lungs, negative pleural pressures
Lowman and Culotta[20] 1945	2,280	F	Cesarean section	Cyanotic, feeble cry, grunting respirations and sternal retraction	Birth	At birth, bilateral	Conservative	Died at 24 hr.	Atelectasis, bilateral pneumothorax
Salmon et al.[27] 1947	3,000	F	Version and extraction	Poor, cyanotic, resuscitation difficult	Birth	5 hr., left pneumothorax; 10 hr., left tension pneumothorax	Aspiration and water trap	Died at 16 hr.	Pulmonary interstitial emphysema
Salmon et al.[27] 1947	3,930	M	Spontaneous	Satisfactory	6 da., dyspnea and cyanosis	12 da., left tension pneumothorax	Aspirations, repeated: mediastinal and pleural	Died at 12 da.	Tension left pneumothorax and small right pneumothorax, patchy atelectasis
Salmon et al.[27] 1947	3,500	M	Spontaneous	Poor respirations established in 2 hr.	Birth	12 hr., bilateral	Aspirations, repeated: mediastinal and pleural	Died at 17 hr.	Tension left pneumothorax, right pneumothorax, mediastinal emphysema, pulmonary interstitial emphysema
Boyette[6] 1949	3,585	M	Home delivery, spontaneous	Good	Cyanotic soon after birth	36 hr., left tension	Aspiration with constant suction	Died at 39 hr.	No autopsy
Borne et al.[37] 1955	1,830	F	Precipitous delivery	Cried almost immediately	22 hr., cyanosis, acute respiratory distress	22 hr., right tension with mediastinal emphysema	Antibiotics, oxygen, aspiration with underwater drainage 1 da.	Survived; pneumothorax and pneumomediastinum subsided on 4th da. of life	Laryngoscopy at onset of symptoms revealed large plug of mucus in trachea

by Holz,[14] Hotz,[15] and Riedweg[22] should not be considered as unequivocal cases of pneumothorax. All these infants survived irrespective of the type of treatment used. Summaries of the nine cases of bilateral pneumothorax without tension in the first ten days of life are presented in Table II; four of these infants died. Table III lists the nine previously reported cases of tension pneumothorax spontaneously occurring in the newborn infant. Four of the nine infants with tension pneumothorax also had bilateral involvement. Five of these nine cases of pneumothorax were accompanied by pulmonary emphysema. All previously reported cases of tension pneumothorax in the newborn, except one, died. Six were treated by thoracentesis and four had thoracentesis with underwater air trap, or constant suction. The sole surviving infant was treated with underwater air trap, oxygen, and antibiotics.

NEW CASES REPORTED

Table IV presents the eight cases of spontaneous pneumothorax in the newborn seen in the Los Angeles Childrens Hospital from 1946 through 1955 plus one other previously unreported case seen by us at the 4450th USAF Hospital. All except one infant had onset of respiratory symptoms within the first 12 hours of life. Six of the infants had complicated delivery, with two of these being delivered by cesarean section. Films of eight of the nine patients were available for review. Four patients (Cases 1, 2, 3, 4) fitted the criteria outlined earlier for proved tension pneumothorax and the three survivors of these four had thoracentesis with continuous underwater drainage for periods of two to four days. Patient 1 had aspiration and underwater drainage for eight hours on the second day of life—then none until four hours prior to death. Patient 8 had a small pneumothorax with all the roentgenologic signs of tension in slight degree (e.g., mediastinal shift, widening of the intercostal spaces, depression of the diaphragm) and the pneumothorax subsided without specific treatment within forty-eight hours. Patients 6 and 7 showed small pneumothoraces, mediastinal shift, and widened intercostal spaces without depression of the diaphragm and the pneumothorax subsided within three days without aspiration. Patient 5 had bilateral pneumothorax with mediastinal emphysema and died before thoracentesis was performed. Films of patient in Case 9 were not available for review. In all surviving infants the pneumothorax had disappeared within four days and usually within two days. Drainage of the pleural space by an underwater trap relieved the tension aspect of the pneumothorax in every instance.

ETIOLOGY

Etiology and etiological classifications have been discussed by Biering,[5] DeCosta,[8] Elkin,[10] Rothman,[25] Hamman,[38] and Salmon and associates.[27] One of our patients had mediastinal emphysema and two others had emphysema of the lung on the side of the pneumothorax. These cases might support the etiological sequence of pulmonary interstitial emphysema, followed by mediastinal emphysema and rupture of the mediastinal pleura into the pleural cavities as proposed by Hamman[38] and Salmon and coworkers.[27] Experimental evidence of

TABLE IV. SPONTANEOUS PNEUMOTHORAX IN THE FIRST TEN DAYS OF LIFE
(NEW CASES NOT PREVIOUSLY REPORTED)

CASE NO. DATE	WEIGHT (GRAMS)	SEX	CONDITION AT BIRTH	ONSET OF RESPIRATORY SYMPTOMS	DIAGNOSIS AND TYPE	TREATMENT	TERMINATION	REMARKS
Case 1 1951	Term length 47½ cm.	M	Good initially	Cyanosis shortly after birth	28 hr., left, proved tension	Oxygen, aspiration with underwater trap at 31-39 and 62 hr.	Died at 66 hr.	Improved after initial aspiration so it was discontinued; became moribund at 62 hr.; post mortem showed atelectasis, bronchopneumonia, and hyaline membrane
Case 2 1953	3,420	M	Cesarean, cyanotic, dyspneic	Birth	1 da., left, proved tension	Oxygen, aspiration, and underwater trap from 36-84 hr.	Survived; reexpanded by 2 da.	Portable chest film initially; bilateral atelectatic areas cleared as did local emphysema on left
Case 3 1955	1,932	F	Twin, 2nd, pink, slight sternal retraction	9 da., sudden retractions after regurgitation	10 da., right, proved tension; 11 da., left, proved tension	Oxygen, single aspiration of right; repeated aspirations and underwater drainage of left 12-16 da. of age; antibiotics	Survived; reexpanded by 13 da. of life	Twin died suddenly at 1½ da. of age, and autopsy (not opened under water) revealed very small pia-arachnoid hemorrhage
Case 4 1955	3,720	M	Normal	1 hr., apneic, cyanotic	2 hr., bilateral proved tension	Aspirated twice, then underwater trap at 5 hr. for 2 da.	Survived; reexpanded by 4 da.	Apneic at 1 hr. and received positive pressure artificial respiration through endotracheal tube until spontaneous respirations recurred following aspiration of pneumothorax

Case 5 1946	3,000	M	Precipitous labor (2½ hr.), lusty spontaneous cry	2 hr., cyanosis, marked respiratory distress	31 hr., bilateral with mediastinal emphysema	Conservative	Died at 36 hr.	Multiple ecchymotic areas were present; post mortem showed early bronchopneumonia, pulmonary atelectasis, and pulmonary hemorrhage in addition to mediastinal emphysema, and subcutaneous emphysema of the neck
Case 6 1949	3,780	M	Good	Less than 4 hr., cyanosis and respiratory distress	8 hr., right, small suspected tension	Conservative	Survived; pneumothorax subsided in 2 da.	Portable chest film initially
Case 7 1953	3,300	M	Face presentation, spontaneous respiration	12 hr., rapid respirations, cyanosis	1 da., left, small suspected tension	Conservative and antibiotics	Survived; pneumothorax subsided at 4 da.	Tracheal catheter used at birth; chest films showed atelectasis in right lung and emphysema of left lung
Case 8 1953	3,435	F	Abruptio placenta; normal, apparently	1 hr., grunting respirations	7 hr., left, small suspected tension	Conservative	Survived; pneumothorax subsided at 2 da.	Bloody meconium (maternal blood)
Case 9 1949	3,060	M	Cesarean; cyanotic	Birth	1 da., left; no tension mentioned	Oxygen; aspiration one time 75 c.c. air	Survived; pneumothorax subsided by 2½ da.	Films not available for review

the interstitial transport of air along vessel sheaves to the mediastinum has been presented by Macklin.[39] The mediastinal pleura requires less tension to rupture than the visceral pleura experimentally.[38]

TREATMENT

Air in the pleural space is unphysiologic but will be removed without aspiration if there is no continuing pleural leakage. With evidence of increasing or tension pneumothorax in any neonate, thoracentesis and continuous drainage by way of an underwater trap should be done. Tension pneumothorax, as described in the previous literature, has almost always been fatal and cannot be regarded lightly. However, aspiration of the pleural cavity cannot be expected to have an effect on pulmonary interstitial emphysema, mediastinal emphysema, hyaline membrane disease, or aspiration pneumonia, if these conditions constitute the primary pathology.

Glaser[40] recommends that tension pneumothorax in older infants can many times be treated conservatively without aspiration. DeCosta[8] recommends prompt aspiration if the pneumothorax be sudden in onset and accompanied by severe symptoms.

SUMMARY AND CONCLUSIONS

1. The incidence of spontaneous pneumothorax of the newborn of clinical significance is probably about 0.07 per cent.

2. Alternating, bilateral, and tension pneumothorax previously reported are reviewed and nine previously unreported cases of spontaneous pneumothorax in the newborn are presented.

3. Etiology and treatment are discussed. Prompt aspiration and continuous drainage by underwater trap is recommended for all patients with tension pneumothorax.

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ABSORPTION OF ACETYLSULFISOXAZOLE LIPID EMULSION

Significant Blood Levels on a Twice-Daily Dosage Schedule

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IN ORDER to achieve significant blood levels with aqueous sulfonamide suspensions it is necessary to administer them at four- to six-hour intervals. In the hospital this entails awakening a child at least once or twice. In the home this schedule imposes a hardship on both the parents and the child. An oral sulfonamide suspension, which can be given every twelve hours, has obvious practical advantages.

The rationale for the use of a lipid emulsion vehicle for sulfonamides stems from a report in 1940 by Feinstone and associates.[1] They described the treatment of experimental infections in mice with sulfonamides, comparing the effect of two suspensions: (1) acacia, and (2) olive oil. The oily sulfonamide suspension was superior as judged by an increased absorption (higher blood levels) and an enhanced therapeutic effect. These observations were recently confirmed by Stephens and Henrickson.[2] They extended the studies to patients who developed therapeutic blood levels following twice-daily dosage of a triple sulfonamide in an oral fat emulsion.

This report will describe the absorption of acetylsulfisoxazole lipid emulsion* as measured by blood levels in children.

MATERIALS AND METHODS

The acetylsulfisoxazole in a highly emulsified vegetable oil base* was supplied for this study in two concentrations: (1) a 10 per cent suspension with 5 c.c. equivalent to 0.5 Gm. of sulfisoxazole in the N_1-acetyl form, and (2) a 20 per cent suspension with 5 c.c. equivalent to 1 Gm. The latter concentration was used exclusively in the last half of the study. These preparations were administered to sixty-seven infants and children 3 months to 12 years of age. The average age for the group was 2.6 years.

Six patients were placed on a single-dose schedule of 75 mg. per kilogram of body weight; and six were given 150 mg. per kilogram. Blood levels were determined at two-, four-, eight-, twelve-, and twenty-four-hour intervals.

Fifty patients received the acetylsulfisoxazole lipid emulsion in a dose of 100 mg. per kilogram every twelve hours for two doses. Bloods were obtained at two, four, eight, twelve, sixteen, and twenty-four hours after the first dose. A series of 200 determinations was performed on this group.

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*Lipo Gantrisin Acetyl, Hoffmann-La Roche, Inc.

The samples were obtained by collecting blood by means of the finger- or heel-puncture technique. They were analyzed for free sulfisoxazole by a modification of the Bratton and Marshall method.[3]

RESULTS

The average blood levels of free sulfisoxazole in twelve children who received the lipid emulsion in single doses of 75 mg. and 150 mg. per kilogram are shown in Fig. 1. The mean peak levels for both groups at four hours were 12.6 mg. per cent and 16.6 mg. per cent, respectively. The twelve-hour levels were 6.2 mg. per cent for the lower dosage and 8.8 mg. per cent for the higher.

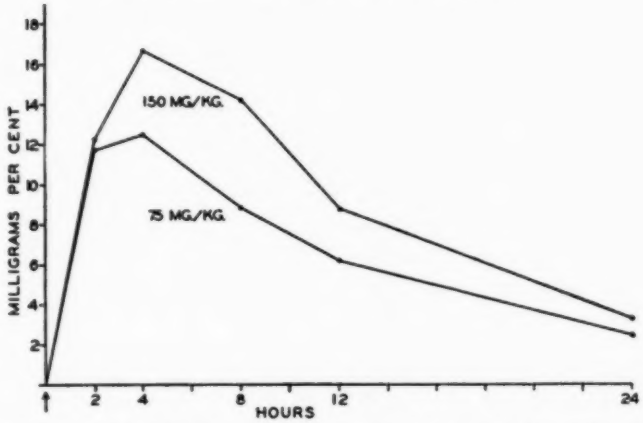

Fig. 1.—Blood levels of free sulfisoxazole in a group of twelve children—six for each dosage schedule.

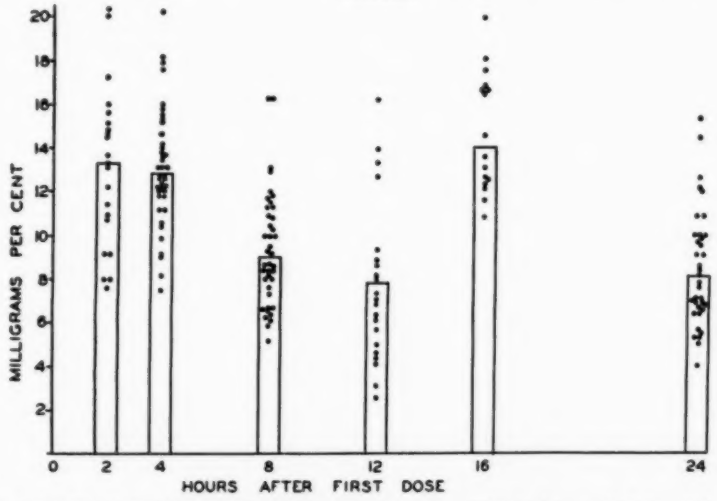

Fig. 2.—Blood levels of free sulfisoxazole on a multiple-dose schedule, 100 mg. per kilogram of weight every twelve hours. Each dot represents one determination. The top of each bar represents the average level.

Fig. 2 illustrates the blood levels obtained on a multiple-dose schedule. Fifty children were given acetylsulfisoxazole lipid emulsion, 100 mg. per kilogram, for two doses at twelve-hour intervals. The tops of the bars represent the average blood levels obtained over a twenty-four-hour period. These mean levels ranged between a high of 14.1 mg. per cent and a low of 7.8 mg. per cent. The 200 determinations are plotted in Fig. 2 as black dots which illustrate the range in blood levels for each sample period during the twenty-four hours.

COMMENT

This study has confirmed the observation of others[1, 2] who have reported enhanced absorption and prolonged effective blood levels following administration of sulfonamides in a lipid emulsion. An oral lipid emulsion of acetylsulfisoxazole produced significant blood levels in a group of fifty children on a dosage schedule of 100 mg. per kilogram every twelve hours.

No untoward effects were noted in the patients who received the suspension.

SUMMARY

1. Acetylsulfisoxazole (Gantrisin) lipid emulsion was administered orally to sixty-seven children ranging from 3 months to 12 years of age. The mean age was 2.6 years.

2. Blood levels were determined following single- and multiple-dose schedules.

3. A single dose of 75 or 150 mg. per kilogram of body weight produced significant blood levels for at least twelve hours.

4. A dose of 100 mg. per kilogram every twelve hours for two doses yielded significant blood levels for the full twenty-four-hour period.

5. No untoward effects were noted in the group of children studied.

We are grateful to Mrs. Audrey Boyer for her invaluable technical assistance.

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THE USE OF DERMAL CONFIGURATIONS IN THE DIAGNOSIS OF MONGOLISM

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IT IS frequently difficult on the basis of clinical evidence to reach a decision as to whether or not a child is a mongoloid imbecile, particularly in the case of a newborn infant. Any additional evidence that can be used is therefore most desirable, especially if this evidence is purely objective. Exactly this sort of objective evidence is to be found in an analysis of the finger, palm, and sole patterns, which vary significantly in their frequencies for mongoloid imbeciles as compared with a control series. The present paper discusses a method by which one can arrive objectively at a calculated index or score. The method is here illustrated by calculations based on studies of 150 certified mongols (the majority of whom are living in institutions) and 540 members of a control series. It will be shown that 70 per cent of the mongoloid imbeciles possess combinations of patterns not repeated in the nonmongol, while 76 per cent of the nonmongols have combinations not found among the imbeciles.

EMBRYOLOGICAL DEVELOPMENT OF DERMAL CONFIGURATIONS

The dermal configurations are formed at the sites of mounds present during the early months of fetal development. These mounds are situated on the tips of the digits, in the four interdigital areas of the palm and sole, as well as in the thenar and hypothenar areas. In addition there is on the sole the calcar mound. During the third and fourth fetal months the mounds are receding at the same time as the dermal ridges are being formed. The interplay of the two processes gives rise to the distinctive patterns found in these areas.[3] Disturbances of fetal growth during the third and fourth months are recorded in the configurations. The configurations once established never change (except in size) during fetal life to birth, nor from birth to death.

METHOD OF PRINTING

Methods of printing infants are outlined in the accompanying article.[4]

DIGITAL PATTERNS

For convenience the digital patterns are here classified into four types: arch, loop ulnar, loop radial, and whorl. The whorls include double loops and all patterns with two triradii. (See Fig. 1.)

In a random series of normal individuals it can be clearly demonstrated that each digit of each hand has a different distribution of patterns (Table I). The second digit (or forefinger) is the most variable, showing in this particular series the

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following percentage frequencies of patterns on the left hand: whorl 33.4, loop ulnar 36.3, loop radial 19.4, arch 10.9. The fifth digit is the least variable: whorl 12.0; loop ulnar 85.4, loop radial 0.0, arch 2.6.

The distribution of the digital patterns on each of the ten fingers of mongols compared with normals shows marked differences, with an over-all increase in ulnar loops, as well as an increase in radial loops on the fourth and fifth digits (Table I).

Differences in the frequencies of patterns can be demonstrated on the left forefinger as follows:

PATTERN	MONGOLS	CONTROL
Whorl	11.9	33.4
Ulnar loop	82.4	36.3
Radial loop	2.3	19.4
Arch	3.4	10.9

The argument and method used throughout the paper can now be

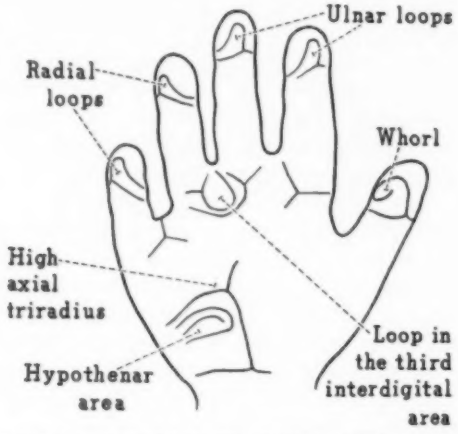

Fig. 1.—Outline of palm of a mongoloid imbecile, showing certain digital and palmar patterns.

TABLE I. COMPARISON OF PERCENTAGE FREQUENCIES OF DIGITAL PATTERNS OF MONGOLOID IMBECILES AND CONTROLS

Percentages for mongoloids based on the finger patterns of 177 imbeciles, of which 54 were reported by Cummins[2]; percentages for controls based on a random group of 328 individuals. Sexes approximately equal in both cases.

Left Digits

PATTERN	V		IV		III		II		I	
	MON.	CON.	MON.	CON.	MON.	CON.	MON.	CON.	MON.	CON.
W	18.3	12.0	32.8	36.9	13.6	17.4	11.9	33.4	22.4	30.8
U	77.1	85.4	58.7	60.2	83.5	71.4	82.4	36.3	73.0	62.7
R	2.9	0.1*	5.1	0.9	1.7	2.6	2.3	19.4	0.6	0.8
A	1.7	2.6	3.4	3.0	1.1	8.6	3.4	10.9	4.0	5.8

Right Digits

PATTERN	I		II		III		IV		V	
	MON.	CON.	MON.	CON.	MON.	CON.	MON.	CON.	MON.	CON.
W	25.9	38.6	14.9	35.7	11.3	19.4	31.8	46.6	18.9	14.6
U	70.6	57.3	82.3	31.1	86.4	70.9	60.2	52.0	75.4	84.0
R	0.1*	0.8	1.7	20.3	1.1	3.4	5.7	0.3	4.6	0.3
A	3.5	3.3	1.1	12.9	1.1	6.3	2.3	1.1	1.1	1.1

*Assigned value.
Symbols: W, whorl; U, loop ulnar; R, loop radial; A, arch.

illustrated. I am indebted to Dr. L. S. Penrose for the original suggestion and to Prof. D. B. W. Reid for further advice. The argument is this: The probability that a child is a mongoloid imbecile is dependent upon the ratio of the frequency of the patterns in mongols and in controls. The greater the ratio the more likely it is that the individual who exhibits the characteristic is a mongoloid imbecile. This ratio may then be taken as an index of the "probability." For example, take one finger of an individual (such as the left forefinger), and if the pattern on this finger is an ulnar loop, then the index is 82.4:36.3 or 2.27. Should the pattern be a loop radial, the index is 2.3:19.4 or 0.12. Similarly, the argument follows for the other patterns of this digit and for the remaining digits (see Table II). It is assumed that the occurrence of each pattern on the ten digits is an independent event. For ease in calculations of the product of the ten indices and recording in histograms, the indices given in Table II are expressed as logarithms in Table III. A histogram based on the digital patterns alone is shown in Fig. 2.

TABLE II. INDICES BASED ON THE FREQUENCIES OF MONGOLOID/NORMAL DIGITAL PATTERNS

	LEFT DIGITS					RIGHT DIGITS				
PATTERNS	V	IV	III	II	I	I	II	III	IV	V
W	1.53	0.89	0.78	0.36	0.73	0.67	0.42	0.58	0.68	1.29
U	0.90	0.97	1.17	2.27	1.16	1.23	2.65	1.22	1.16	0.90
R	29.00*	5.67	0.65	0.12	0.75	0.13*	0.08	0.32	19.00	15.33
A	0.65	1.70	0.13	0.31	0.69	1.06	0.09	0.17	2.09	1.10

*Based on assigned value.
Symbols: W, whorl; U, loop ulnar; R, loop radial; A, arch.

TABLE III. INDICES BASED ON THE FREQUENCIES OF MONGOLOID/NORMALS DIGITAL PATTERNS, EXPRESSED AS LOGARITHMS

Left Digits

PATTERNS	V	IV	III	II	I
Whorl	0.1847	$\bar{1}$.9494	$\bar{1}$.8921	$\bar{1}$.5563	$\bar{1}$.8633
Ulnar loop	$\bar{1}$.9542	$\bar{1}$.9868	0.0682	0.3560	0.0645
Radial loop	1.4624*	0.7536	$\bar{1}$.8129	$\bar{1}$.0792	$\bar{1}$.8751
Arch	$\bar{1}$.8129	0.2304	$\bar{1}$.1139	$\bar{1}$.4914	$\bar{1}$.8388

Right Digits

PATTERNS	I	II	III	IV	V
Whorl	$\bar{1}$.8261	$\bar{1}$.6232	$\bar{1}$.7634	$\bar{1}$.8325	0.1106
Ulnar loop	0.0899	0.4232	0.0864	0.0645	$\bar{1}$.9542
Radial loop	$\bar{1}$.1139*	$\bar{2}$.9031	$\bar{1}$.5051	1.2788	1.1855
Arch	0.0253	$\bar{2}$.9542	$\bar{1}$.2304	0.3201	0.0414

*Based in part on an assigned frequency.

PALMAR CONFIGURATIONS

Of the palmar patterns, those of two areas are found to be particularly useful. The first concerns the size of the hypothenar patterns as measured by the height of the distal axial triradius. In general, one may say that 85 per cent of the palms of mongoloid imbeciles have a large hypothenar pattern terminated distally by a high axial triradius (t″) (Fig. 1). A pattern of this size is found in about 12 per cent of the palms of nonmongols.

To determine the position of the distal axial triradius, measurements are made (1) of the distance between the triradius and the distal wrist crease, (2) of the length of the palm from the distal wrist crease to the proximal crease of the middle finger. The height of the triradius is then calculated as a percentage of the palm length. Triradii in low positions, from 0 to 14.9 per cent, are symbolized by t; those in intermediate positions, from 15 to 39.9 per cent, as t′; those in high positions, from 40.0 per cent and up, as t″.

Calculated unilaterally, a high axial triradius (t″) is found in mongols on 85.8 per cent of left palms, 84.4 per cent of right palms; while in the control series the percentages are 10.2 per cent on the left, 13.3 per cent on the right. Low and intermediate triradii are grouped together and comprise the remaining percentage in each case.

The second palmar configuration is that present in the third interdigital area (Fig. 1). Fang[5] has shown a significantly higher frequency of patterns in this area among mongoloid imbeciles compared with the general British population. In our series of mongoloid imbeciles the frequency of true patterns (L, D, W) is approximately the same as in Fang's series (left palm 54.0 compared with 51.7; right palm 85.4 compared with 82.4), but the frequencies of these same pat-

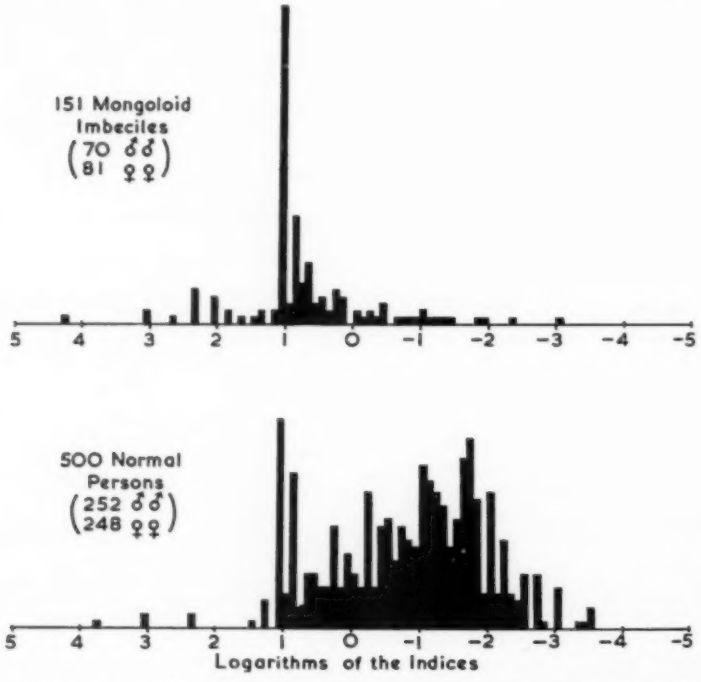

Fig. 2.—Histograms showing distributions of indices for the digital patterns alone of 151 mongoloid imbeciles and 500 controls.

terns for the two general populations vary widely (left palm, 31.3 for Toronto compared with 23.2 for the British; right palm, 55.5 compared with 48.2) (Table IV). These differences are probably due to the more mixed racial population of Toronto. Since the formulations of vestigial patterns compared with "open fields" tend to be subjective rather than objective, we prefer to base our calculations on the summed frequencies of "true patterns" (L, D, W) versus "not true patterns" (L^v, V, O) (Table IV).

For the palmar patterns the same argument is used in a continued calculation of the index. For example, if a true pattern is present in the left third interdigital area, the "probability" is greater that the individual is a mongol rather than a nonmongol and the index is 54.0:31.3 or 1.8.

Table IV. Comparison of Percentage Frequencies of Third Interdigital Configurations In Mongoloid Imbeciles and Controls

(Sexes in each group approximately equal)

Configurations	Left Palm		Right Palm	
	Mongols (150)	Controls (1,000)	Mongols (150)	Controls (1,000)
Loop (L)	54.0	29.9	84.7	53.6
Loop with accessory triradius (D)	---	1.0	0.7	1.7
Whorl (W)	---	0.4	---	0.2
Loop vestigial (L^v)	3.3	2.5	3.3	1.4
Vestige (V)	14.7	14.6	2.0	4.3
Open field (O)	28.0	51.6	9.3	38.8
Summary				
True patterns (L, D, W)	54.0	31.3	85.4	55.5
Not true patterns (L^v, V, O)	46.0	68.7	14.6	44.5

Plantar Configurations

The most useful of all the dermal configurations are the patterns in the hallucal area of the sole. On nearly half of the left or the right soles of mongoloid imbeciles the pattern found is an arch tibial, while in nonmongols this pattern occurs on about one in 200 right or left feet (Table V).

Conversely, whorls have a low frequency among mongols (left 0.9, right 2.6), but a much higher frequency among controls (left 32.4, right 27.1).

Loop distal patterns, if considered without regard to size of pattern, show approximately the same frequencies for mongoloids and controls (*left sole*, mongols 46.6 per cent, controls 51.4 per cent; *right sole*, mongols 44.8 per cent, controls 57.1 per cent). However, as a loop distal pattern becomes smaller it gradually merges into an arch tibial (Fig. 3), and it is these smaller loops which are found more commonly among mongols. The size of the pattern is measured by counting the number of dermal ridges between the core of the pattern and its triradius. When loop distal patterns are divided into *small loops* with twenty or less ridges, and *large loops* with twenty-one ridges or more, the frequencies of distribution for small loops are:

	Left	*Right*
Mongols	33.8%	31.2%
Controls	9.6%	11.7%

Final Calculation of Index

Combining the "probabilities" based on the configurations of these selected digital, palmar, and plantar areas, a

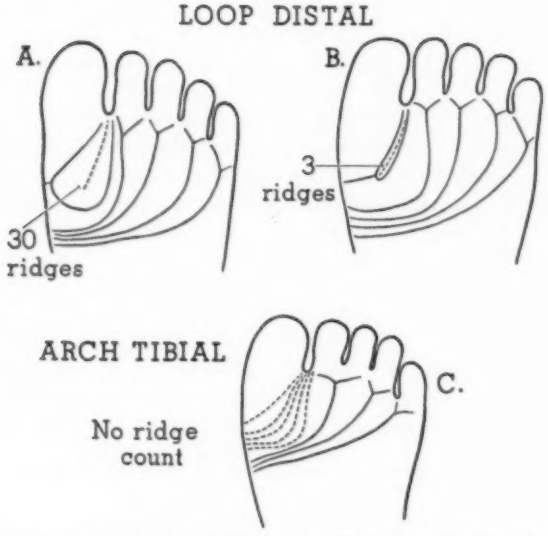

Fig. 3.—Outlines of soles of mongoloid imbeciles, showing large and small loop distal hallucal patterns, the latter compared with an arch tibial pattern.

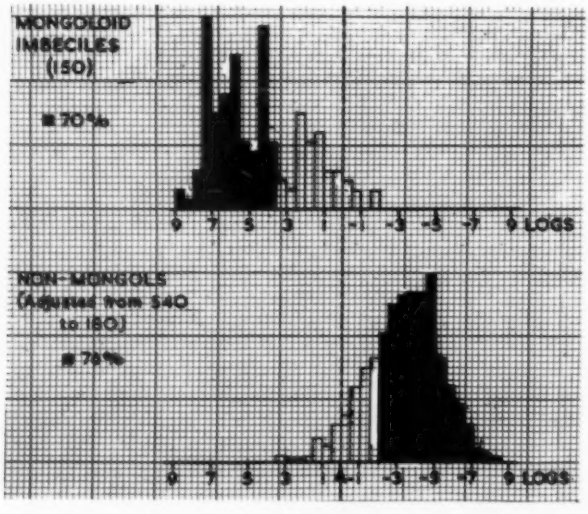

Fig. 4.—Histograms showing distributions of indices for the combined digital, palmar, and plantar patterns of 150 mongoloid imbeciles and 540 controls.

single score or index is obtained. Fig. 4 shows histograms based on the analysis of 150 mongoloid imbeciles and 540 controls. An example of the calculations for a mongol and a university student are shown in Table VI.

The control series of 540 individuals (Fig. 4) includes 130 twins, 85 epileptics (approximately half of whom were mentally defective), and 57 patients with rheumatic fever. The remainder were students (secondary

TABLE V. PERCENTAGE OCCURRENCE OF HALLUCAL PATTERNS IN MONGOLOID IMBECILES COMPARED WITH CONTROLS

	NUMBER OF PERSONS		TYPE OF HALLUCAL PATTERN									
			A^t	RIDGE COUNT L^d 0-20	RIDGE COUNT 21-	$_vL^d$	L^t	W	TA	A^f	L^f	o/o
Mongols	116 (62 ♀ ♀) (54 ♂ ♂)	Left sole	46.6	33.8	12.7	3.4	2.6	0.9				
		Right sole	47.4	31.2	13.6	3.4	0.9	2.6	0.9			
Controls	210 (164 ♀ ♀) (46 ♂ ♂)	Left sole	0.5	9.6	41.8		10.5	32.4		1.4	0.9	2.9
		Right sole	0.5	11.7	45.4		10.5	27.1		1.4	0.5	2.9

Symbols: A^t, arch tibial; L^d, loop distal; $_vL^d$, vestigial loop distal; L^t, loop tibial; W, whorls; TA, tented arch; A^f, arch fibular; L^f, loop fibular; o/o, open field.

TABLE VI

Digital patterns of mongoloid imbecile:

LEFT					RIGHT					INDEX
5	4	3	2	1	1	2	3	4	5	
U	R	U	U	U	U	U	U	U	U	6.5

Symbols: U, loop ulnar; R, loop radial.

Complete index for mongoloid imbecile:

Digital		Palmar (Axial triradii)			Palmar (3rd interdigital configurations)				Plantar (Hallucal pattern)				
		Lt.		Rt.	Lt.		Rt.		Lt.		Rt.	Index	(Log.)
6.5	×	85.8 / 10.2	×	84.4 / 13.3	×	54.0 / 31.3	×	85.4 / 55.5	×	46.6 / 0.5	×	47.4 / 0.5	=	7.91

Digital patterns of university student:

LEFT					RIGHT					INDEX
5	4	3	2	1	1	2	3	4	5	
U	U	U	R	U	W	U	U	U	U	0.3

Symbols: U, loop ulnar; R, loop radial; W, whorl.

Complete index for university student:

Digital		Palmar (Axial triradii)			Palmar (3rd interdigital configurations)				Plantar (Hallucal pattern)				
		Lt.		Rt.	Lt.		Rt.		Lt.		Rt.	Index	(Log.)
0.3	×	14.2 / 89.8	×	15.6 / 86.7	×	46.0 / 68.7	×	14.6 / 44.5	×	2.6 / 10.5	×	0.9 / 10.5	=	$\bar{5}.63$ or -4.37

school and university) and other persons taken at random. None of these groups plotted individually nor combined showed a distribution of indices approaching that of the group of mongoloid imbeciles.

There still remains the problem of the overlap between the mongols and controls, and in future calculations we plan to use additional characters such as the presence of a single crease on the fifth digit, the single simian crease on the palm and the speckling of the iris. With the addition of these and other characters it is hoped that the overlap will be reduced. We are also testing for the association of patterns.

PRACTICAL APPLICATIONS

The practical applications of these findings are:

1. To supply additional evidence for the diagnosis of mongolism in the newborn infant and to leave on file objective documentary evidence which will never change throughout the life of the individual.

2. To contribute evidence in cases of disagreement regarding the diagnosis of mongolism.

3. To convince parents that the disturbance of growth in their defective mongoloid child began at least five to six months before birth; that it was not due to any accident of birth or illness in infancy and that the damage is so extensive that treatment is probably of little avail.

SUMMARY

1. A new method is outlined by which a purely objective diagnosis of mongolism can be made.

2. The method is based on the significant differences in the frequencies of dermal configurations for mongoloid imbeciles compared with a control series.

3. It is shown that 70 per cent of mongoloid imbeciles possess combinations of patterns not repeated in nonmongols, while 76 per cent of the nonmongols have combinations not found among the imbeciles.

4. The dermal configurations used are the finger patterns and certain of the palm and sole patterns.

Dr. Harold Cummins of Tulane University was the first to point out the value of dermal configurations in the study of mongoloid imbeciles (1936, 1939). Since that time my graduate students and I have continued to explore this field. I am especially grateful to a number of those who assisted in the collection of prints and in the work of calculations. Acknowledgements are also made to Dr. L. S. Penrose and to the following officials of institutions who most generously assisted in the early stages of the investigation: Dr. Alan Brown and the staff of The Hospital for Sick Children; the late Dr. A. P. Lewis of the Psychiatric Hospital, Toronto; the late Dr. S. J. W. Horne and Mr. H. D. L. Goodfellow of the Ontario Hospital School, Orillia, Ont.; Dr. Elizabeth Nesbitt of the North Jersey Training School, Little Falls, N. J., and to the directors of several private institutions.

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INKLESS METHODS OF FINGER, PALM, AND SOLE PRINTING

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A MODERN and generally acceptable method of taking finger, palm, and sole prints is a chemical one. The materials* consist of sensitized paper and small individual flannel pads damped with a chemical solution. A pad is rubbed over the palm or sole and the chemical solution is then worked well into the skin (as one would rub in a hand lotion). The sensitized paper is placed on a half-inch rubber pad and the palm pressed on it lightly but firmly. To obtain a complete print of an adult, the following procedure is recommended: Ask the person to relax. Holding the hand by the finger tips, touch first the wrist to the paper, then gradually lower the hand and fingers. Press at the base of the fingers (with the side of your hand), press in the middle of the hand (with your fist), press lightly on the tips of the fingers, roll the thumb over once and release, and finally raise the hand from the thumb side, rolling the hand over on its ulnar edge (Fig. 1, *A-E*). Remove hand. By this procedure all the ridged skin can be printed on the sensitized paper, although the skin is scarcely, if at all, discolored.

For a child's hand very little pressure is needed and one must be careful to keep the prints light and clear. When printing an infant wait until the hand relaxes naturally, and then press the palm against the paper which, in this case, is held in your hand on a small, thin (quarter-inch) rubber pad. With some infants it may be necessary to hold the hand open with your fingers, as shown in Fig. 2, *B*.

The fingerprints will frequently be completely recorded when the general palm print is made. In the case of infants, if the fingerprints are not clear or complete, use narrow strips of Faurot paper. Holding a strip on your hand or forefinger, take a series of rolled prints of each finger (Fig. 2, *C*). For adults the regular fingerprinting procedure is followed, using Faurot materials instead of ink.

For plantar prints the toes should be turned well back and the sensitized paper, held on a thin rubber pad, is pressed well in at the base of the digits and then pressed along the sole.

The older ink method can be used, but it makes the printing of palms and soles much more difficult. In an emergency prints can be made by rubbing face cream into the skin, touching the palm or sole to highly

From the Department of Zoology, University of Toronto, and The Research Institute of The Hospital for Sick Children.

*Materials can be purchased from Faurot Inc., 299 Broadway, New York 7, N. Y.

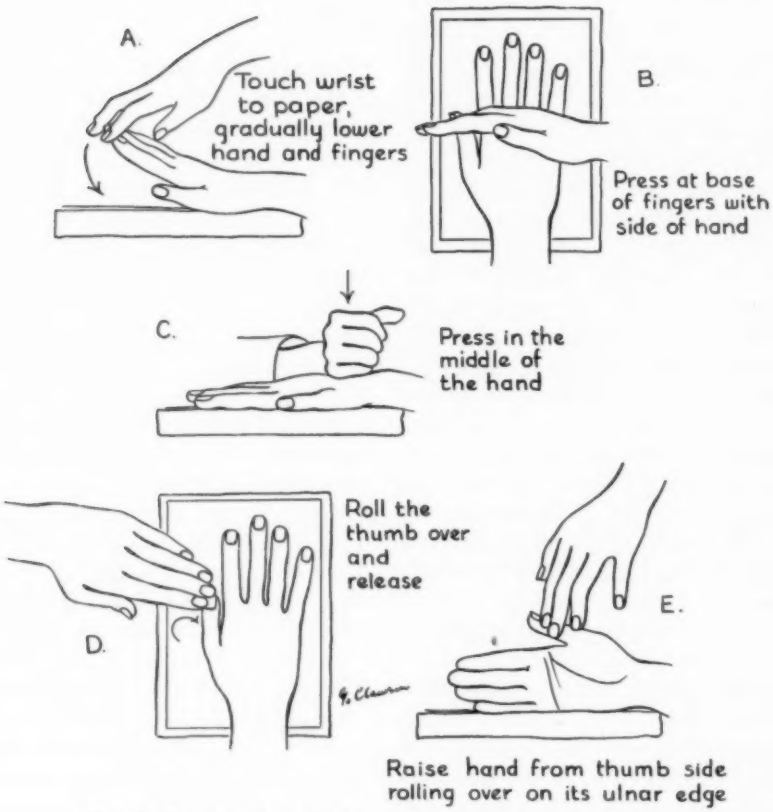
A.
Touch wrist to paper, gradually lower hand and fingers
B.
Press at base of fingers with side of hand
C.
Press in the middle of the hand
D.
Roll the thumb over and release
E.
Raise hand from thumb side rolling over on its ulnar edge

Fig. 1.—Procedure for taking complete palm print of an adult.

glossed paper, dusting the print with lamp black and fixing it with shellac. Or a print can be taken on smoked paper and fixed with shellac.

the prints are "lifted" with Scotch tape. For adults the latter method is good, but it is difficult to get sharp prints with young infants.

A. Holding baby's relaxed hand by wrist, make print swiftly while hand is unclenched.
B. Grasp infant's wrist in left hand, slip right index finger under infant's curled fingers and place your other fingers at back of hand.
C. Roll each digit separately on small narrow strips

Fig. 2.—Procedure for taking palm prints and fingerprints of an infant.

Cotterman[1] outlined a method by which the skin ridges are painted with fountain pen ink or India ink and

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CONGENITAL CHOLEDOCHAL CYSTS

A Report of Three Cases and Discussion of Etiology

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Pittsburgh, Pa.

VATER, according to Blocker and associates,[5] reported the first case of choledochal cyst in 1793. Since then there have been numerous reviews concerning this entity,[2, 11, 18, 19, 32] the latest being that of Tsardokas and Ronett.[25] The youngest on record was a fetus[9] and the oldest, a patient 62 years of age.[10]

In the period from June, 1945, to January, 1956, there were three patients with choledochal cysts among more than 50,000 patients who were admitted to Children's Hospital of Pittsburgh. These three cases added to those previously reported[2, 9, 10, 17, 25, 26, 31, 32] bring the total to 242.

CASE REPORTS

Case 1.—C. E., a 4½-year-old white female, was admitted to Children's Hospital in November, 1945, because of nervousness and irritability which were present for several months. Prior to admission she was seen by her family physician, who noted, on routine examination, distention of the right side of the abdomen. Physical examination revealed a smooth, sharply defined mass, predominantly in the right upper quadrant. The mass was presumed to be the liver.

On roentgen examination, the mass seemed to be separate from the liver. Barium roentgen studies (Fig. 1) revealed a displacement of the second portion of the duodenum to the left by a mass which was apparently extrinsic to the gastrointestinal tract. Intramuscular pyelogram was not remarkable. Hemogram was normal.

Twelve days after admission, at laparotomy, a large cystic mass, 10 by 8 by 6 cm., was found. The cyst was attached at its upper pole to both the cystic and the enlarged common hepatic duct; and at its lower pole, to a small common bile duct and hence to the second part of the duodenum. This was dissected free and excised (Fig. 2). The hepatic duct was then anastomosed to the distal third of the stomach. As the abdomen was closed, the child suddenly ceased to breathe.

Case 2.—M. H., a 10-month-old white female, was first seen at 3 months of age in the Children's Hospital outpatient department because of intermittent clay-colored stools and dark urine for three weeks. At the time, a yellow tint was noted in the skin, but this decreased steadily in intensity. Three days prior to her first clinic visit, the family physician found bile in her urine. The mother stated that intravenous fluids had been administered because of the right upper quadrant pain and vomiting for one week. Family history revealed that two of the four other siblings had branchial cleft cysts. Physical examination revealed an alert child with minimal icterus of the selerae and skin, a few small scattered petechiae of the abdominal wall, and a small patent orifice on the right side of the neck. Hemoglobin

From the Children's Hospital of Pittsburgh and the Department of Pediatrics, University of Pittsburgh School of Medicine.

was 8.2 grams per cent with 2,900,000 red blood cells, and 13,750 white blood cells (polymorphonuclears 55, lymphocytes 45). A Coombs test was negative. Liver studies after admission (see Table I) were normal except for a bilirubin of 2.95 mg. per cent, with 2.40 mg. per cent free bilirubin, and a total protein of 5.90 grams per cent, with 2.09 grams per cent globulin. The child was transfused with 100 ml. of packed cells, and discharged with the diagnosis of anemia of undetermined etiology.

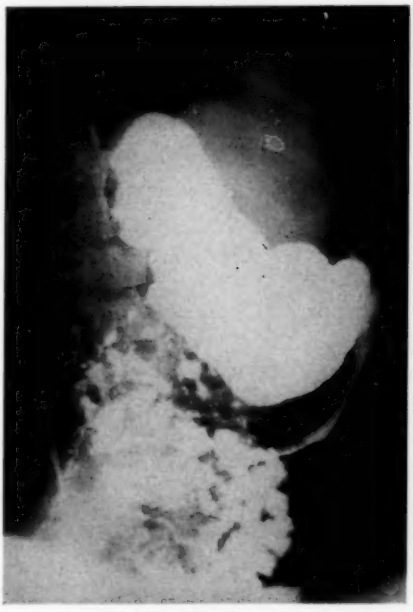


Fig. 1.—Gastrointestinal series film demonstrating anterior displacement of the duodenum with pressure in the duodenal loop and downward displacement of the small bowel.

She was readmitted one month later because of light stools, dark urine, and poor weight gain. Physical examination was not remarkable except for the opening at the right side of the neck at the middle of the sternocleidomastoid muscle. Blood studies at this time revealed hemoglobin 10 grams per cent and 3,500,000 red blood cells. While hospitalized, her stools were normal. Liver function was improved (see Table I). The child was discharged with the diagnosis of subsiding hepatitis.

Six months later the child was admitted for the third time because she continued to have intermittent light stools and dark urine. Four days prior to admission, jaundice and increased irritability were noted. Physical examination was unchanged except that a large, spherical, smooth, compressible cystic mass was found in the right upper quadrant, extending to the midline at the level of the umbilicus and under the liver. The tip of the spleen was also palpable. Sclerae were icteric. Hemoglobin was 10 grams per cent and red blood

Fig. 2.—Choledochal cyst, 10 by 8 by 6 cm., removed at operation as described in Case 1.

count was 3,700,000. Bone marrow aspiration indicated only mild iron deficiency. Roentgen studies showed a normal intravenous pyelogram, an unsuccessful cholecystogram, and anterior displacement of the first and second portions of the duodenum, with widening and impingement on the lateral border of the duodenal loop in the gastrointestinal series

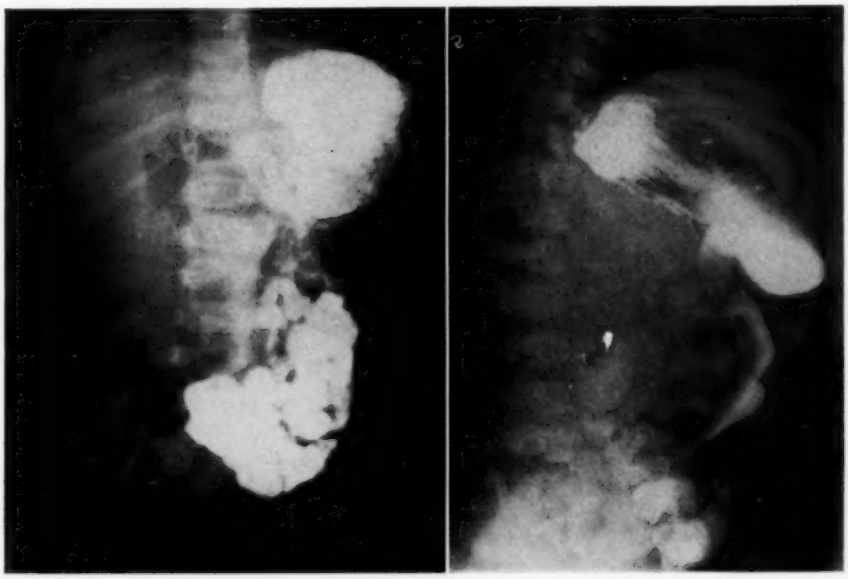
TABLE I

DATE	PLASMA PROTHROMBIN TIME %	BILIRUBIN TOTAL	BILIRUBIN FREE	BILIRUBIN BOUND	TOTAL PROTEIN	ALB.	GLOB.	CEPH. FLOC.	THYM. TURB. M.L.U.	ALK. PHOS. B.U.	URINE UROBILINOGEN	URINE BILE
12/14-17/54	100	2.95	2.40	0.55	5.9	3.8	2.1	48 hr. 1+	0.5			
1/17-22/55		<0.05						48 hr. ±	0.5		Neg.	Neg.
7/19/55		9.65	7.60	2.05	7.40	3.57	3.83	48 hr. ±	2.5	38.3	T	Pos.
7/21/55	65											
7/26/55		1.00										

(Fig. 3). Chemical studies revealed liver function tests compatible with an obstructive type of jaundice (see Table I). Because of the finding of obstructive jaundice, the patient was operated upon four days after admission, with a preoperative diagnosis of (1) retroperitoneal cystic teratoma, or (2) choledochal cyst.

A large cystic mass, containing bile, was found to fill the right upper quadrant. This was traced to the common and cystic ducts. The cyst was decompressed and anastomosed to the second portion of the duodenum directly. The postoperative course was benign. Within four days the bilirubin fell to 1.00 mg. per cent. Study of the biopsy of the cyst wall revealed a specimen 2.0 mm. thick, which had fragmented columnar epithelium on one surface. The remainder of the wall was dense collagenous scar.

The child was discharged on the eleventh postoperative day. By three weeks her jaundice had completely cleared. Six months after operation the child was well.



A. *B.*

Fig. 3.—Roentgen films from Case 2, showing displacement of the small bowel downward and to the left (*A*) and anterior displacement of the duodenum (*B*).

CASE 3.—B. H., a 14-month-old white female, was admitted with the complaints of a rash for three weeks, diarrhea for three weeks, and jaundice for one week. Past history and family history were negative except for the older sibling's having had rubella during the sixth fetal month. Growth and development had been normal. About three weeks prior to admission to Children's Hospital the child awoke in the morning with a bumpy rash on the cheeks, body, hands, and, most severely, on the buttocks. This was treated with no success. The child became irritable at nights when the rash seemed to be more severe. The following day the child passed dark amber, foul-smelling urine and about eight to nine light yellow, soft, foul-smelling stools. About two weeks after the onset she was admit-

TABLE II

DATE	BILIRUBIN			PROTHROMBIN TIME		URINE BILE	URO-BILINO-GEN	STOOL BILE	CEPH. FLOC.	THYM. TURB. M.L.U.	ALK. PHOS.	RBC	Hb
	TOTAL	FREE	BOUND	CONT.	PATIENT								
8/6	17.1	14.4	2.7										
8/7												3.6	10.2
8/8	21.3	16.6	4.7	12 sec.	12 sec.	Pos.			Neg.	1			
8/10							Neg.	Neg.					
8/15	4.7	4.2	0.5			Pos.							
8/17	9.1	7.3	1.8					Neg.					
8/19												3.0	9.5
8/23	7.10	4.8	2.3										
8/27	2.2	1.7	0.5	13 sec.	13 sec.				±	2.5	8.4		

ted to another hospital. At that time her stools were reduced to three per day. Three days later (five days prior to admission) the child was noted to have yellow sclerae and, one day later, yellow skin. Two days prior to admission, the child spiked a fever of 104° F. and had an episode of rapid breathing. Jaundice seemed to be deepening. Appetite remained good.

Physical examination revealed an irritable, white female with icteric skin and sclerae. A maculopapular eruption was noted on the skin with numerous excoriations. Liver was palpated four fingerbreaths below costal margin. Rectal examination revealed clay-colored feces. Measurements varied between the tenth and seventy-fifth percentile for a female one year of age.

The child's jaundice started to subside and the color of the feces returned to normal. Laboratory data (Table II) indicated an obstructive type of jaundice with subsiding obstruction. The child ran a low-grade fever for three days.

Jaundice, however, increased again. At this time it was noted that the liver was only about one fingerbreadth below the right costal margin, and that there was a large cystic mass under it, filling the entire right upper quadrant. Gastrointestinal series (Fig. 4) indicated that there was anterior displacement of the second portion of the duodenum and compression of the loop. At laparotomy a medium grapefruit-sized choledochal cyst (Fig. 5) was found and anastomosed directly to the adjacent duodenum. This child made an uneventful recovery. Postoperatively the jaundice subsided (Table II) and the child was discharged on the twelfth postoperative day. Four months after operation the child was doing well.

Fig. 4.—Widening and impingement on the lateral border of the duodenal loop, with anterior displacement of the first and second portions of the duodenum.

Fig. 5.—The grapefruit-sized cystic mass seen at laparotomy, below the liver and gall bladder.

DISCUSSION

All of the above patients were young females with evidence of a

mass in the right upper quadrant. Jaundice presented in two of the three cases and pain, or at least discomfort, in two. In these cases the usual incidence of abdominal tumor, jaundice, and abdominal pain or the combination of all three (abdominal mass 80 per cent, jaundice 75 per cent, abdominal pain 60 per cent, triad 60 per cent) is approximated.[2, 13] With the presence of these symptoms and signs, the diagnosis of choledochal cyst should be considered. A cholecystogram, which usually shows no function but which may show function,[8, 14, 29] and a gastrointestinal series which indicates anterior displacement of the gastrointestinal tract (as in the accompanying figures) are the two most helpful diagnostic x-ray features. Liver function studies which indicate obstructive rather than hepatocellular disease are also useful.

Early surgical intervention seems to be the treatment of choice when a choledochal cyst is found. As has been shown by others, extirpation of the cyst is frequently fatal.[9] This was true in the case at Children's Hospital of Pittsburgh. However, the mechanism of death here was undetermined because no post-mortem examination was done. The procedure of choice seems to be either a cystoduodenostomy or a Roux-en-Y procedure.[1, 6, 7, 13, 19, 21, 23, 24] Patients who are not operated upon seem to succumb early.

Cysts have varied in size from 30 ml.[18] to over 8 liters.[13] The cyst walls have been reported to range from 1 mm.[10] to 7.5 mm.[18, 32] in thickness. Usually the histology of the cyst wall is similar to that of the common bile duct.

ETIOLOGY

Congenital choledochal cysts are localized dilatations of the common bile duct which usually occur at the junction of the common hepatic and cystic ducts; however, they may be anywhere along the choledochus. In true congenital cysts, no acquired cause, such as obstructions due to stones or tumors, can be found. Sometimes cystic dilatations may be superimposed upon generalized enlargement of the biliary tree. Multiple etiological factors have been enumerated[2, 3, 10, 11, 14, 16, 18, 20, 27, 28, 30, 32] and discussed in detail by others. The etiology most commonly accepted as correct today is that advanced by Yotuyanagi,[30] who postulated that there was unequal proliferation at the stage of physiologic occlusion of the choledochus, with resulting enlargement at the time of recanalization. However, he states that there must also be a second factor—that of obstruction. Gross[11] feels that there must be weakness of the duct wall associated with obstruction.

If there is obstruction, could not sudden increases in pressure due to contraction of the biliary tree be responsible for the localized dilatation of the ductus choledochus similar to the dilatation of a balloon when it is first inflated? The pressure exerted by the gall bladder, or against which bile can be secreted, may be as great as 250 to 300 mm. of water.[4] The obstruction could be due to an atresia, stenosis of the ducts with partial or complete occlusion, or achalasia of the sphincter of Oddi. Valvelike folds are commonly found at the orifice at the lower pole of the cyst. These could be formed by the weight

of the cyst as it grows larger, angulating the duct and consequently causing further obstruction.

SUMMARY

Three cases of choledochal cysts are added to the English literature, bringing the total number of authentic cases to 242. Of these, 178 had an abdominal mass, 167 jaundice, and 129 abdominal pain. The urinary and blood chemistry findings most commonly associated with this disease entity indicate an obstructive rather than hepatocellular type jaundice. Cholecystogram is usually negative and gastrointestinal series show displacement of the duodenum anteriorly and to the left. The most efficacious therapeutic procedure usually is cystoduodenostomy or Roux-en-Y anastomosis of the cyst to the jejunum. Etiology is discussed with the added hypothesis of sudden increases in pressure in a partially or completely occluded duct being the cause of the initial dilatation.

I wish to express my appreciation to Dr. Stuart S. Stevenson for his aid and encouragement in the preparation of this paper. These cases are presented with the courteous permission of Drs. H. H. Finlay, W. B. Kiesewetter, E. S. A. King, E. R. McCluskey, and W. K. Sieber.

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Corkscrew Therapy

The very best assistant in this way to the irruption of the teeth is a cork. Take a cork screw and worm it into a new cork of a proper size to be admitted with ease into the mouth, and you have a play thing both useful and pleasing to the child; the soft and spongy nature of the cork is exactly suited to the tender state of the gums, and is unattended by the danger inseparable from permitting such young infants to chew a crust of bread, which is often recommended; but they too frequently get off large pieces, which might be productive of fatal consequences unless great attention was paid, and this cannot always be obtained from ordinary attendants: and the ivory or ebony head of the common cork screw I believe equally good as the coral, when a more polished substance is required; and if of gold or silver, they are still better. I have observed an infant set several minutes at one time and bite the cork, with evident tokens of pleasure, while his little hands were busily employed playing with the cork screw.

THE MATERNAL PHYSICIAN, New York, 1811.

OBSERVATIONS ON THE CLINICAL USE OF V-CILLIN* IN PEDIATRIC PRACTICE

M. Alvarez-Pagan, M.D., D. C. Rees, M.D., and G. F. Conway, M.D.

THE Pennsylvania State College released a report[1] in 1945 covering observations on penicillin biosyntheses following the introduction of various precursors, among which was phenoxyacetic acid, into synthetic media. Behrens and co-workers[2] in 1948 reported the preparation of the sodium salt of phenoxymethyl penicillin. Further studies by Brandl and associates[3, 4] demonstrated the acid stability of phenoxymethyl penicillin (penicillin V).

Since earlier studies[5] had indicated that part of the loss of activity of orally administered benzyl penicillin (penicillin G) was due to inactivation by acid hydrolysis while in the stomach, the possible therapeutic advantages of an acid-stable compound were apparent. The greater absorption of penicillin V after oral administration was demonstrated[6-10] and its antimicrobial activity was found to parallel closely that of penicillin G.[8, 11]

METHODS AND RESULTS

Because of the advantages of oral administration of medication, especially in the pediatric age group, we decided, when a suitable oral preparation became available, to make a clinical trial of penicillin V in a general pediatric clinic practice. A series of eighty-four patients, ranging in age from 5 months to 12 years, was studied. With the exception of eight, who were hospitalized, these patients were all treated on an outpatient basis. All suffered from respiratory tract infections. The only criteria for inclusion in the group given oral penicillin V were that the child have an infection for which he would ordinarily be given antibiotic therapy, that he be ill enough so that he ordinarily would have been given multiple injections of procaine penicillin G, and that he exhibit sufficient objective signs of illness to reveal the effect of therapy. The drug was not administered to children considered to have viral infections, nor as a "prophylactic" measure. Routine laboratory studies included a complete blood count and bacterial culture of the throat with one exception, in which case drainage from the middle ear was cultured. Chest x-rays were obtained as clinically indicated. No attempts were made to obtain antibiotic sensitivities on the isolated bacteria.

The dosage of penicillin V was, with few exceptions 250 mg. (400,000 units) stat and 125 mg. (200,000 units) q. 4 h. or q.i.d. given for three to four days. The patients listed as showing "satisfactory" responses received a second three-day course of

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*V-Cillin Suspension; fruit-flavored pediatric oral suspension of penicillin V, Lilly.

therapy, as did those listed as "unsatisfactory" (Tables I, II, III). The dosage schedule used in this study was considered typical of that used in outpatient practice daily. It should be pointed out that the American Heart Association is advocating in the treatment of streptococcal infections that the therapeutic dosage of penicillin V be continued for at least ten days.

In sixty-five of the eighty-four patients, the results of therapy, as judged by defervescence, physical findings, and general clinical response, were considered good or excellent. The response was considered "satisfactory" in twelve patients and "unsatisfactory" or a "therapeutic failure" in only seven. We were impressed by the rapid relief of pain in patients with otitis media, and with the very rapid fall in temperature observed in most patients, particularly in those who appeared more acutely and severely ill.

TABLE I. THERAPEUTIC RESULTS IN AND ORGANISMS ISOLATED FROM FIFTY-THREE PATIENTS WITH ACUTE TONSILLITIS OR PHARYNGITIS

	ORGANISM ISOLATED FROM THROAT SWABS						
THERAPEUTIC RESULT	ALPHA HEMOLYTIC STREPTOCOCCUS	BETA HEMOLYTIC STREPTOCOCCUS	STAPHYLOCOCCUS AUREUS	PNEUMOCOCCUS	NO CULTURE	NORMAL FLORA	TOTAL
Unsatisfactory or poor	1	3				2*	6
Satisfactory	2						2
Good	19	6	2		4	3	34
Excellent	3	6	1	2	4		16

*One patient developed measles.

TABLE II. THERAPEUTIC RESULTS IN AND ORGANISMS ISOLATED FROM TWENTY PATIENTS WITH OTITIS MEDIA

	ORGANISM ISOLATED FROM THROAT SWABS						
THERAPEUTIC RESULT	ALPHA HEMOLYTIC STREPTOCOCCUS	BETA HEMOLYTIC STREPTOCOCCUS	STAPHYLOCOCCUS AUREUS	PNEUMOCOCCUS	NO CULTURE	NORMAL FLORA	TOTAL
Unsatisfactory or poor		1					1
Satisfactory	1	3	2			2	8
Good	2	2	1		1	1	7
Excellent	2*	2					4

*Organism cultured from middle ear drainage in one patient.

TABLE III. THERAPEUTIC RESULTS IN AND ORGANISMS ISOLATED FROM SIX PATIENTS WITH LARYNGOTRACHEOBRONCHITIS (LTB) AND FIVE PATIENTS WITH BRONCHOPNEUMONIA (BPN)

	ORGANISM ISOLATED FROM THROAT SWABS						
THERAPEUTIC RESULT	ALPHA HEMOLYTIC STREPTOCOCCUS	BETA HEMOLYTIC STREPTOCOCCUS	STAPHYLOCOCCUS AUREUS	PNEUMOCOCCUS	NO CULTURE	NORMAL FLORA	TOTAL
Unsatisfactory or poor							0
Satisfactory			1 LTB	1 LTB			2 LTB
Good	1 BPN			1 LTB		2 LTB	3 LTB 1 BPN
Excellent	1 BPN 1 LTB	2 BPN				1 BPN	1 LTB 4 BPN

The therapeutic response as determined objectively was, perhaps, less striking in laryngotracheobronchitis and otitis media, although these patients usually were rapidly improved symptomatically.

In several cases the organisms isolated probably represented the normal nasopharyngeal flora. In these patients the illness may have been of viral etiology, or perhaps the pathogenic organism was missed. The therapeutic response was generally good in these cases.

The preparation used was well accepted and taken by all except one child who refused it. Gastric upset, which required discontinuance of therapy, and which may have been due to the drug, was reported in two instances. Mild diarrhea was reported in three patients and pink urine considered to be due to the coloring agent in two patients.*

Two examples of typical cases follow.

CASE REPORTS

A. W., a 19-month-old Negro child, was admitted on Jan. 16, 1956, because of high temperature. About three days prior to admission he had developed a slight, nonproductive cough which gradually increased in severity. On the day of admission he became febrile and rather listless. Breathing became slightly laborious several hours prior to admission.

Physical examination on admission revealed an acutely ill 19-month-old Negro boy with a temperature of 105.6° F., rectally. His respirations were counted at 76 per minute. There was marked pharyngeal injection and a few minute yellowish tonsillar follicles. The neck was flaccid and there was no lymphadenopathy. There was slight diminution in breath sounds at the right upper side of the chest anteriorly.

X-ray of the chest taken immediately upon admission showed a pneumonic infiltrate involving the right upper lobe. White blood cell count done at that time revealed 26,750 white blood cells, with a differential showing 81 per cent neutrophils, 18 per cent lymphocytes, and 1 per cent monocytes. A throat culture grew out hemolytic *Staphylococcus aureus* and a beta hemolytic streptococcus. Upon admission the patient was started on V-Cillin, 250 mg. stat and 125 mg. every four hours. A dramatic improvement was observed, the fever subsiding in six hours and remaining normal thereafter. About sixteen hours after admission the white blood count was 14,950, with 76 per cent neutrophils, 20 per cent lymphocytes, and 4 per cent monocytes. At that time respirations seemed normal and were counted at 42 per minute. Three days after therapy was started x-ray revealed almost complete disappearance of the pneumonic process in the right upper lobe. The patient was discharged on January 19, completely asymptomatic.

J. S., a 6-year-old white boy, was admitted March 6, 1956, with history of a sore throat for five days, swelling in right cervical area, of one day's duration, and fever for a few hours prior to admission.

On physical examination he appeared febrile (103° F., orally), the posterior pharynx was markedly injected and coated with yellowish exudate, and the anterior cervical triangle lymph nodes were extremely tender and markedly enlarged bilaterally, more on the right. The spleen was not felt.

A blood count performed on admission revealed 29,100 white blood cells with 90 per cent polymorphonuclears and 10 per cent lymphocytes. V-Cillin therapy was started with 250 mg. as initial dose and 125 mg. q. 4 h. On the second hospital day the white blood

*The use of this dye has been discontinued and a harmless, metabolized, vegetable dye substituted.

count was 22,700, with 79 per cent polymorphonuclears and 19 per cent lymphocytes, 1 per cent monocytes and 1 per cent basophils. The temperat : was still elevated and symptoms were still marked, so it was decided to double the dosage. By the third hospital day the temperature was down to normal and improvement proceeded rapidly.

DISCUSSION

An oral suspension of penicillin V was found to be well accepted and tolerated without notable side effects by seventy-eight of our group of eighty-four patients. Penicillin V proved to be clinically effective in combating the respiratory tract infections due to hemolytic streptococci, *Staphylococcus aureus*, and *Diplococcus pneumoniae*. Our results compared favorably with those which might have been expected from the intramuscular administration of 300,000 units of procaine penicillin G twice daily to the same patients. Consequently we feel that in children the majority of respiratory infections requiring penicillin therapy may be treated successfully with oral penicillin V.

Since the blood level of penicillin V begins to decline after four hours, with detectable levels remaining six hours after oral administration,[12] we elected to give 250 mg. (400,000 units) as the initial dose and 125 mg. (200,000 units) q. 4 h. or q.i.d. Thus the acid stability of penicillin V makes it possible, practicably, to obtain consistently high blood levels soon after oral administration and to maintain therapeutically effective levels by regular q. 4 h. to q. 6 h. dosage. This allows one to treat effectively and practicably children who have penicillin-susceptible infections, by the oral route, without the need for multiple injections. In addition to the more apparent advantages to the oral route of treatment, the decreased risk of inducing penicillin-sensitivity in the child[13] must be considered.

SUMMARY

A well-accepted pediatric oral suspension of penicillin V was used to treat respiratory tract infections in eighty-four children observed in a general pediatric clinic practice. The results were quite good. It is concluded that oral penicillin V can be used to treat effectively most of the penicillin-susceptible infections of childhood.

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Early "Shock Treatment"

THE *Chin-cough* is a disease that has hitherto in a great measure eluded the art of medicine: and as it oftentimes proves very stubborn, and gives way very reluctantly, it frequently becomes an object of domestic skill and management. But as none of those familiar domestic means have ever been *really* serviceable, they are better (especially what is made use of as medicine internally) omitted. When the complaint takes a favourable turn, it is frequently attributed to the means that were last used; hence, that means is, ever after, recorded as infallible. —As it is a disease of the spasmodic or convulsive kind, it has been sometimes relieved, or even removed, by a shock or sudden fright:* thus; riding upon a bear (a frightful mode of travelling no doubt,) from the fright it occasions, has been said to be serviceable. Giving the patient a part of some disgustful animal, as a mouse, &c. to eat, and afterwards informing him of it. And so forth. —By way of medicine, the antimonial puke, No. 3. page 158, given every or every other evening, as there directed, will often greatly relieve the complain, and cause the fits of coughing to be less severe and frequent.

**To the Medical Reader.* —Is electricity, in any mode, likely to relieve this disease?

WILLIAM MOSS, 1781.

THE MICROSPECTROPHOTOMETRIC DETERMINATION OF BLOOD OXYGEN SATURATION IN INFANTS AND CHILDREN

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WITH the development by Roos and Rich[1] of a simple, rapid, and reasonably accurate spectrophotometric method for the determination of oxyhemoglobin saturation, it occurred to us that a micrometric adaptation of this technique could be of value to us in the study of certain pediatric conditions, notably the behavior of blood oxygen levels in early neonatal life. It was necessary, first, to determine the feasibility of the technique for the small amounts of blood which can be collected easily from nontraumatic puncture of the newborn infant's heel, and second, to devise a method of collection suitable to the small subject which would maintain the oxygen saturation constant until the time of analysis.

In Roos's method the blood is hemolyzed and diluted in a closed system with a saponin solution of such high alkalinity that the oxyhemoglobin dissociation curve is maximally shifted to the left. The optical density of the blood solution is then read at two wave lengths, and from these two values and the predetermined constants for reduced and oxyhemoglobin at the same wave lengths, the oxyhemoglobin saturation of the sample can be calculated. As only the ratio of the two optical densities of the sample is required, neither the dilution nor the optical pathway need be known exactly, eliminating the need for calibrated cuvettes. The purpose of the dilution is to allow enough light to be transmitted at the selected wave lengths and optical path.

That the oxygen content of arterialized cutaneous blood samples agrees closely with that of those obtained by arterial puncture was first demonstrated by Lundsgaard and Moller[2] in 1922, then by Goldschmidt and Light[3] in 1925, by Lowry and associates[4] in 1942, and by Apgar and co-workers[5] in 1955. None of the various methods for collection of cutaneous blood described by these and other investigators seemed ideally suited to our purpose; hence, another technique was devised.

METHODS

Collection of the Blood.—In newborn infants and those who are not yet walking and in whom the foot is still fleshy and the skin thin, the heel serves as an ideal site for puncture. In older children a finger is more convenient.

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This study was originally supported in part by the Children's Research Foundation, St. Louis, Mo., and later by Research Grant B685 from the National Institute of Neurological Disease and Blindness, of the National Institutes of Health, U. S. Public Health Service, as part of a long-term study of neonatal anoxia.

In newborn and small infants the cutaneous blood of the heel is arterialized prior to puncture by wrapping the foot and leg snugly in a diaper wrung out of hot water, holding about two minutes, and repeating with a fresh, hot diaper. In larger subjects the finger is held in a basin of hot water (45 to 47° C.) for about five minutes, as suggested by Hultgren and Hackett.[7] Not only does this preliminary heating serve to arterialize the blood but also the vasodilatation induced increases the rate of flow, so that the necessary amount (0.2 to 0.5 ml.) can be obtained readily from an ordinary stab, without squeezing or stasis, and without the necessity for a deep cut. This is an important consideration where subsequent samples are desired.

After cleansing, make a brisk stab with a new* No. 11 Bard-Parker blade. In using the infant's heel, hold the ankle in the hollow of the left hand and press the ball of the foot firmly with the thumb. Wipe away the first drop or two of blood and quickly coat the heel very lightly with sterile mineral oil. This channels the drop neatly into the tiny collecting tube and eliminates the smearing which would inevitably alter the oxygen saturation. Hold the specially prepared tube, which has been filled to within a centimeter or two of the brim with mineral oil, as close to the foot as possible, so that the blood drops directly into the oil from a distance of no more than 1 to 2 cm., an exposure which will not change the oxygen content, as shown by Lilienthal and Riley.[6] As the drops settle to the bottom of the tube they may be mixed very gently with the end of a paper clip to ensure heparinization. The procedure may be facilitated if desired by having the baby supported so that the foot remains in a dependent position. Following collection place the specimen upright in a small rack and refrigerate immediately, or place the rack in a small basin of crushed ice for transport as desired. Short exposure of the tubes to temperatures of 70° F. or less do not affect the oxygen saturation. We were able to keep the refrigerated samples for several hours or even overnight without altering their oxygen content appreciably.

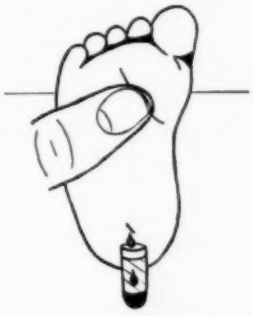

Fig. 1.—Drops of blood falling through mineral oil into collecting tube. (Note position of thumb on ball of foot.)

The tubes used for collection are of ordinary soft glass about 1½ inches in length, which are siliconized with Dri-film,* rinsed thoroughly, inverted in a rack, and dried. A tiny drop of heparin solution is added, and the tube filled almost to the brim with mineral oil.

Spectrophotometric Analysis.—

I. Apparatus:

1. Spectrophotometer. In these studies a DU model Beckman spectro-

*The technique is made impossible by trying to use blades that have been dulled by routine autoclaving, though they may be cleansed with acetone or alcohol for repeated use in the same subject.

*Dri-film, SC-87, General Electric Company.

photometer with blue-sensitive phototube was used.

2. Cuvettes. Cuvettes of 10 mm. with spacers of 9 mm. were used. For the determination of the original constants, calibrated cuvettes and spacers are needed, since one must know the exact optical pathway for this initial standardization.
3. For the dilution of each specimen a tuberculin syringe (for very small amounts of blood) or a 2 ml. hypodermic syringe, containing a drop of mercury as agitator and fitted with a No. 19 or No. 20 needle is used to secure the blood from beneath the oil in the collecting tube. Following dilution and mixing with the saponin solution, the No. 19 needle is replaced with a bent No. 22 spinal puncture needle, and this is used in filling the cuvette.
4. As a receptacle for the alkaline saponin solution a 50 ml. syringe is used. This is fitted with a three-way B-D stopcock, and the latter attached through a short length of thick-walled rubber tubing to a piece of glass tubing equipped with a rubber pipette tip. (The glass tubing facilitates removal of deaerated saponin solution from the Van Slyke chamber.)

II. Reagents:

These consist of a borate buffer and alkaline saponin solution prepared exactly as described by Roos and Rich.[1]

III. Procedure:

1. Lightly grease the barrel and outside tip of a 2 ml. or tuberculin syringe with petrolatum or mineral oil.
2. Attach a 2 inch No. 19 needle.
3. Draw up 0.2 to 0.3 ml. mercury, pushing out air bubbles and discarding excess in such a way that the needle is filled and a bead of about 0.1 ml. remains in the syringe.
4. Insert mercury-filled needle through the oil to the bottom of the tube and stir blood gently.
5. Slowly draw up 0.1 to 0.4 ml. of blood, being careful not to admit air bubbles to the syringe.
6. Remove needle carefully.
7. With both syringes lying on the table, attach sample syringe to the large saponin receptacle syringe by means of the side opening of the stopcock, having previously expelled a few drops of saponin solution through this route. Dilute the blood with the saponin solution by slowly withdrawing the plunger of the sample syringe until the required volume of saponin has been obtained.

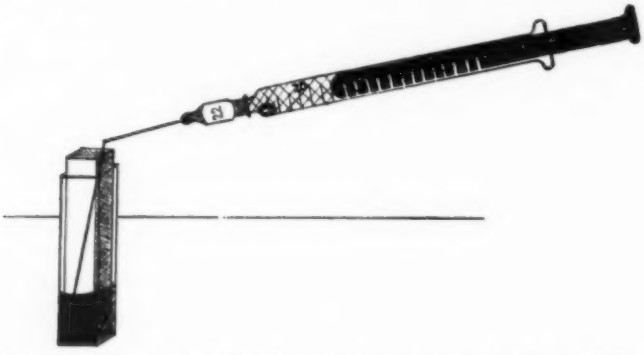

Fig. 2.—Filling the cuvette with diluted sample from syringe fitted with bent needle. The cuvette is filled from the bottom.

Dilution is approximate and depends roughly on the hemoglobin content of the blood. When this is over 15 grams per cent, as in most newborn infants, one part blood and three parts saponin are used. When the hemoglobin content is likely to be under this figure, use one part blood and two parts saponin. For polycythemic blood, one part blood and four parts saponin are used.

8. Remove syringe from stopcock, carefully placing finger over tip. Invert gently two or three times, letting mercury bead mix the blood and saponin solution.
9. Place a 3 inch No. 22 spinal puncture needle, bent to an angle of 30 degrees, on the syringe and expel the first drop or two of solution. Then gently slide the needle down between the cuvette and spacer, allowing the cuvette to fill from the bottom. No oil is necessary, as light passes through the lower portion of the cuvette which is protected from the air by an appreciable column of fluid.
10. As a blank a similar cuvette is filled with the saponin solution, omitting the blood.
11. Read promptly at 600 and 506 mμ. The latter wave length is the isobestic point for reduced and oxyhemoglobin.
12. Calculations:

$$K_1 = \frac{\epsilon_{600Hb}}{\epsilon_{600Hb} - \epsilon_{600HbO_2}} \text{ (in our case 1.520)}$$

$$K_2 = \frac{\epsilon_{506}}{\epsilon_{600Hb} - \epsilon_{600HbO_2}} \text{ (in our case 2.00).}$$

Initial Determination of the Extinction Coefficients.—This procedure must be done with extreme care and accuracy. Since this initial standardization is the area where difficulty is most often encountered, the following technical points have been included:

1. Have about 30 ml. freshly drawn heparinized blood available.
2. Saturate the blood fully by rotating in a Barcroft flask for 10 minutes.
3. Place blood in a small beaker which can be covered with a watch glass.
4. Mix blood thoroughly with a glass rod and remove 1 or 2 ml. with a calibrated Ostwald-Van Slyke pipette, the stopcock of which has been greased.
5. Deliver into a tiny (10 ml.) beaker.
6. With a similar pipette add two parts of saponin. (If 1 ml. of blood has been used, add 2 ml. of saponin.)
7. Place solution in a cuvette of exactly known optical path. (Calibrated cuvette and spacer necessary.)

$$\text{Per cent oxyhemoglobin saturation} = K_1 - \left(\frac{\text{O.D. } 600}{\text{O.D. } 506} \times K_2\right) \times 100$$

For the calculation of K_1 and K_2 the extinction coefficients (ϵ) are determined according to the following formulas. The full derivation of these formulas by Beer's law is contained in the original paper of Roos and Rich.[1]

$$\epsilon_{506} = \text{O.D.}_{506} \times \text{dilution} \times \frac{1}{\text{cuvette} - \text{spacer (in cm.)}} \times \frac{1.67^* \times 1.36^{**}}{O_2 \text{ capacity}} - 0.57\dagger$$

$$\text{and } \epsilon_{600} = \text{O.D.}_{600} \times \text{dilution} \times \frac{1}{\text{cuvette} - \text{spacer (in cm.)}} \times \frac{1.67^* \times 1.36^{**}}{O_2 \text{ capacity}} - 0.57\dagger$$

where

*1.67 is the concentration of HbO_2 per 100 cubic centimeters in millimols per liter.
**1.36 is the amount of oxygen taken up by 1 gram of hemoglobin.
†0.57 is the factor for dissolved oxygen;
then

8. Read optical densities at 600 and 506 mμ. (If possible do in duplicate.)
9. Again mix the blood in the original beaker thoroughly and run oxygen capacity by the Van Slyke-Neill manometric technique. Run duplicate determinations.
10. To the remainder of the blood in the original beaker (do not attempt to transfer aliquots from this beaker) add sodium hyposulfite, a large pinch, or in the proportion of 5 mg. $Na_2S_2O_4$ to 1 ml. of blood. This will reduce the oxyhemoglobin completely.
11. Dilute with saponin as above and determine optical densities of this solution at 600 mμ and 506 mμ in exactly the same manner.

    Note: readings at 506 mμ should be the same for reduced as for oxyhemoglobin, since this is the isobestic point for both compounds.

SUMMARY

A rapid and reasonably accurate (within 5 per cent) method for the microspectrophotometric determination of blood oxygen saturation in infants and children is presented. A technique for blood collection simply performed with a minimum of disturbance and cumbersome impedimenta is described.

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ALKALINE RESISTANT (FETAL) HEMOGLOBIN IN HYPOCHROMIC MICROCYTIC ANEMIAS OF INFANCY AND CHILDHOOD

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IT HAS been stated that small but definitely increased amounts of fetal hemoglobin may occur in nutritional anemias and those caused by toxins that result in iron deficieney.[1, 2] The following study was undertaken to ascertain the range of values of fetal hemoglobin in specific age groups of children with these anemias.

MATERIAL

One hundred two normal infants and children were used as a control group. These varied in age from 4 months to 7 years, and were presumed to be free of hematological disorders as judged by blood examination and the electrophoretic pattern of their hemoglobin.

There were eighteen anemic infants and children who varied in age from 4 to 28 months in our test group. Twelve of these children suffered from some degree of malnutrition caused by an iron-deficient diet plus an infection. Nine of these had upper respiratory disturbances of varying degree. Two had had attacks of prolonged diarrhea, and one had viral hepatitis. Six of the infants were premature. None had any blood transfusions or treatment for their anemia prior to our study. The peripheral blood in all eighteen children was hyperchromic and microcytic with hemoglobin levels of 4.6 grams to 10.8 grams.

From the Department of Pediatrics, University of Illinois College of Medicine.

METHOD

Fetal hemoglobin was determined by the alkali denaturation technique and paper electrophoresis at pH 8.6 of the hemolysate. The method of Singer[3] was used with a very slight modification. It was realized during the process that only a small amount of hemoglobin solution was necessary for the test if the loss of material could be minimized. This loss was avoided by using a 2 cm. diameter microfunnel with filter paper cut to fit for the process of filtering. It was possible to perform four determinations with 1 c.c. of resultant hemoglobin solution. Thus in a mildly anemic infant only 2 to 3 c.c. of oxalated blood was necessary. In the moderately severe, 4 to 5 c.c. was used; and in the severely anemic infant, 7 to 10 c.c. Thus it is not necessary to draw large quantities of blood from small infants.

RESULTS

The results of the study of the anemic children are shown in Table I. The comparison of these results with those in the normal control group is shown in Fig. 1.

TABLE I

DISEASE	AGE (MO.)	TOTAL HEMOGLOBIN, GMS. PER 100 ML.	FETAL HEMOGLOBIN, PER CENT OF TOTAL
1. Malnutrition (hypoplastic marrow)	4	9.5	25.3
2. Prematurity	4½	7.0	10.2
3. Prematurity	5	6.8	8.5
4. Prematurity	5½	6.0	8.0
5. Malnutrition and U.R.I.*	5½	9.4	1.3
6. Malnutrition and U.R.I.	7	9.9	0.9
7. Prematurity	8	7.5	3.0
8. Prematurity	8	8.0	2.0
9. Chronic diarrhea	9	6.5	0.9
10. Malnutrition and U.R.I.	10	8.5	2.5
11. Malnutrition and U.R.I.	11	9.0	0.8
12. Chronic diarrhea	13	6.3	2.4
13. Viral hepatitis	14	8.2	1.48
14. Prematurity and U.R.I.	15	8.5	2.0
15. Malnutrition and U.R.I.	17	10.8	2.0
16. Malnutrition and U.R.I.	19	4.6	1.1
17. Malnutrition and U.R.I.	24	10.4	0.79
18. Malnutrition and U.R.I.	28	8.6	0.0

*U.R.I., upper respiratory infections.

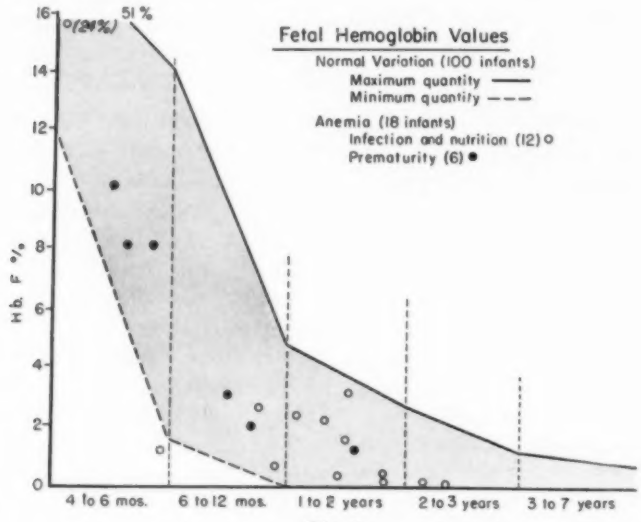

Fig. 1.

DISCUSSION

The fetal hemoglobin values in the normal control group are in good agreement with those of Chernoff and Singer.[3] They state that small amounts (less than 5 per cent) may continue in some normal children to school age.

There was no increase of fetal hemoglobin demonstrable in eighteen instances of hypochromic microcytic anemia. The prematurity of six of these infants was presumed to be the etiological factor of their anemias. Twelve of the infants suffered from malnutrition, with a diet low in iron. The majority of these anemias seemed to follow upper respiratory infections. Two were preceded by a diarrhea of

over two months' standing, and one patient had suffered from three months of jaundice due to a viral hepatitis. The estimated fetal hemoglobin of this group was well within normal limits. They were studied before, during, and after the phase of improvement with iron therapy. No appreciable difference in the level of fetal hemoglobin was noted despite the rise in total hemoglobin.

Bernard and associates[4] produced anemia in rabbits by the toxic action of phenylhydrazine on the marrow, and showed that during the recovery phase there was an increase of alkali-resistant hemoglobin in proportion to the improvement of the general blood picture. This may serve to explain why, in those instances of malnutrition or iron deficiency anemia with a pretreatment level of hemoglobin as low as 4 grams, no increase of alkali-resistant hemoglobin in the recovery phase occurred. There is no impairment of marrow activity and the extramedullary centers are not stimulated.

CONCLUSION

Eighteen infants from 4 to 28 months of age suffering from a hypochromic microcytic anemia, following either prematurity or malnutrition and infection, showed values of fetal hemoglobin that were within the normal limits of their age group.

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Of Tetanick Complaints

Nothing is a more frequent cause of tetanick complaints, than to have nails or splinters of any sort, run into the feet, so as to wound the *involucra* of the tendons, or the *nerves* that are numerously inserted in these parts. I have known the opisthotonus to arise from the extensor tendons of the thumb, being so slightly wounded, by the thorn of an orange tree, that one could scarcely perceive where it entered.

FROM LIONEL CHALMERS: WEATHER AND DISEASES OF SOUTH CAROLINA, 1776.

JAW-WINKING (MARCUS GUNN PHENOMENON)

EARL E. SMITH, M.D., AND M. E. GANS, M.D.
CLEVELAND, OHIO

RECENTLY one of us (E. S.) examined a one-month-old, first-born, white male infant who was normal except for a mild ptosis of the right upper eyelid. The mother stated that she had noticed, shortly after she brought the infant home from the hospital, that the baby's right upper eyelid drooped and that, in the act of sucking the nipple, the right upper eyelid would shoot up. The baby developed normally, both mentally and physically, but the ptosis and winking phenomenon remained the same. At age 6 months the infant was seen by an ophthalmologist (M. G.) who recognized the condition as a case of jaw-winking or Marcus Gunn phenomenon. Fig. 1, *A* demonstrates the infant at age 10 months with a partial ptosis of the right upper eyelid. Fig. 1, *B* reveals the right eyelid retracted on the act of opening the mouth.

There are no other cases in the family and subsequently a second child, female, was born with no abnormalities other than mild erythroblastosis, requiring no transfusion.

ETIOLOGY

Jaw-winking or Marcus Gunn phenomenon was first described by an English ophthalmologist, Dr. Marcus Gunn, in 1883. This phenomenon has since been observed by many ophthalmologists in the United States and elsewhere.

About 2 per cent of all cases of congenital ptosis are due to this condition. Males are more frequently affected than females, and the left upper eyelid more frequently than the right. Heredity seems to play a part in the jaw-winking phenomenon. It has been noticed in a mother and son, and in two out of six siblings, one of whom had an affected child. It has also been observed in two brothers. The "Marcus Gunn phenomenon" may begin in later life following an injury or disease.

Many theories have been proposed to explain the jaw-winking phenomenon. The most commonly accepted hypothesis is that the levator palpebrae muscle is connected, not only with the third nucleus, but also with the external pterygoid portion of the fifth nucleus.

SYMPTOMS

Although this condition usually persists into adult life, it is most marked in infancy when the rapid spasmodic movements of the lid are apparent during sucking and thus are noticed soon after birth. It is typically unilateral and is associated with ptosis, but rarely with any other muscle anomaly of the eyes. All degrees of the condition are seen and, since only those who wish relief come

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to notice, it is probable that many of the minor cases are missed.

In its fully developed form, the upper lid, when at rest, covers the upper half of the cornea in a condition of partial ptosis, but when the lid to be raised. As a general rule, if the jaw is deviated toward the opposite side, a maximal retraction occurs.

The description of the "inverted Marcus Gunn phenomenon," described by Marin Amat in 1918, is of interest. In this condition, when the patient started to chew, tears flowed from his right eye and the eye closed automatically when he opened his jaw is opened, the apparently paretic upper lid shoots upward to a level higher than that of the other eye; on attempting to look upward the mouth is usually opened, thus allowing the

A. *B.*

Fig. 1.—*A*, Infant at age 10 months, with a partial ptosis of the right upper eyelid. *B*, Right eyelid retracted on the act of opening the mouth.

A. *B.*

Fig. 2.—Jaw-winking in a 19-year-old girl.

mouth or while chewing. Amat assumed that a peripheral anastomosis existed between the fifth and seventh nerves.

TREATMENT

Treatment of the mild cases is not indicated. Where the condition is unsightly, surgery may be indicated. This consists of complete section of the levator and the utilization of the superior rectus to raise and control the upper lid. Grant corrected the phenomenon by cutting the motor root of the trigeminal nerve.

SUMMARY

A congenital anomaly of the eyelid, resulting in an unusual clinical manifestation, the so-called jaw-winking phenomenon, is presented.

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ADDENDUM

Since this article was submitted, a young lady, aged 19, presented herself at the office of one of us (M. E. G.) who had been following her case since childhood. Her pictures are included, as they show the phenomenon better than those of the infant. Fig. 2, *A* demonstrates the ptosis of the right upper eyelid. Fig. 2, *B* reveals the eyelid elevated during the process of chewing.

THE VALUE OF TRANSILLUMINATION IN THE DIAGNOSIS OF HYDRANENCEPHALY

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THE purpose of this report is to present a case of hydranencephaly and the use of transillumination of the cranial vault in establishing the diagnosis. Hydranencephaly implies a loss or failure of development of cerebral tissue and with this a prognostication is inherent. The outlook for the condition is grave. To be able to forewarn of this eventuality is the principal concern of the physician regarding this entity at the present time.

CASE REPORT

The patient, a white male infant, was born Dec. 6, 1953, a product of a normal pregnancy and spontaneous delivery without complications. The birth weight was 8 pounds 8 ounces. The remainder of the historical data revealed no pertinent findings referable to the infant's subsequent condition. On December 23, at the age of 17 days, the infant was brought to the hospital because the mother noted that the head seemed to be getting large. No other complaints were registered about the baby and no pertinent information was elicited. Birth measurements other than that of the birth weight were not known by the mother nor were they obtainable.

Physical examination revealed a white male infant in no acute distress. He was well developed but appeared somewhat inactive. The head was dolichocephalic in shape, the anterior fontanel was bulging, the posterior fontanel was open, and the cranial sutures were separated. Head circumference was 38.5 cm. (50th percentile = 35.4 cm.), and chest circumference, 33 cm. (50th percentile = 33 cm.). The eyes revealed a bilateral red reflex, pupils reacted to light, there was an intermittent horizontal nystagmus, and a left internal strabismus. The neck was supple, and no opisthotonus was noted. Ear, nose, and throat examination was negative, as well as that of the chest, abdomen, genitals, back, and extremities. The Moro reflex was physiologic. Bilateral Babinski was present. No hypo- or hypertonicity was observed. Patellar reflexes were "brisk." No bony abnormalities or congenital defects were noted. The cry and color were good; weight at the time of admission was 7 pounds, 12½ ounces. A diagnosis of early hydrocephaly was considered, with a possible subdural hematoma.

Hospital Course.—The baby was in the hospital for five weeks, during which time he ate poorly and was supported by intravenous fluid therapy. He vomited on occasion and this was attributed to increased intracranial pressure. The skin was noted to be cold to touch in the area of the trunk and extremities. The temperature varied from as low as 95° F. on the twelfth hospital day to a 104° F. spike on the twenty-fourth hospital day, for which no cause could be found. During the second hospital week the extremities became spastic and rigid. The thighs were flexed on the abdomen. The fists were clenched so tightly that the palmar surface began to ulcerate. Because of the generally poor condition and low temperature, prophylactic

From the Cook County Hospital.

penicillin was started, daily, intramuscularly, and the baby was placed in a heat cradle.

Laboratory Studies.—These included a skull roentgenogram which showed separation of the sutures. Roentgenograms of the chest and abdomen were negative. On Jan. 4, 1954, hemoglobin and the red blood count were elevated, 14.8 grams and 6.09 million per cubic millimeter, respectively. The white blood count was 20,850 with a differential that was normal except for 7 eosinophils. Blood chemistries on Jan. 4, and Jan. 8, 1954, were: sodium, 169 meq. per liter; chloride, 131 meq. per liter; potassium, 4.5 meq. per liter; and sodium, 154 meq. per liter; chloride, 115 meq. per liter; potassium, 4.9 meq. per liter, respectively. On January 4, blood culture revealed no growth. A subdural tap was performed and 30 c.c. of straw-colored fluid was removed. Chemically there was 1,000 mg. per cent protein and glucose was negative. Subdural hematoma with membrane formation was suspected and it was decided to hydrate the baby and operate. A right parietal burr hole was made January 15, which revealed a subdural membrane. Needle puncture secured some yellow-colored fluid. The membrane was incised and several hundred cubic centimeters of fluid came forth. A probe was inserted into the cranial vault and could be passed without opposition to the opposite side. No falx cerebri was encountered. The only cerebral tissue made out at surgery was a small amount on the floor of the cranial cavity (Fig. 1). The baby survived the procedure and existed vegetatively for twelve days postoperatively with supportive care of fluids, antibiotics and warmth. *Post-mortem examination* was done, including examination of the cranial vault. When the cranium was opened, about 600 c.c. of dark brown fluid was removed. The cerebral hemispheres were virtually absent and were reduced to a thin membrane which was tightly adherent to bony structures. The third ventricle and aqueduct were obliterated, being surrounded by merely a small amount of atrophic brain parenchyma. Bronchopneumonia was also present.

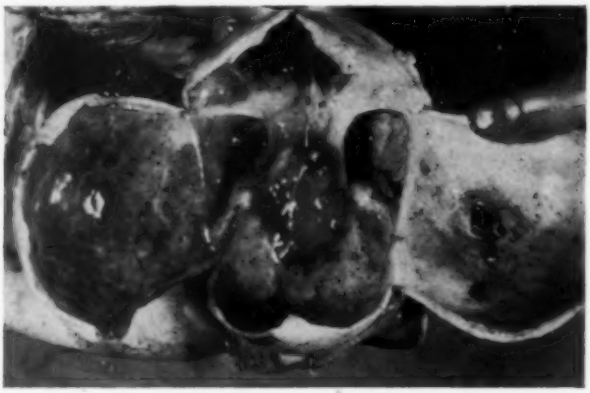

Fig. 1.—Post-mortem cranial vault. Paucity of cerebral tissue.

DISCUSSION

The diagnosis of hydranencephaly can be suspected early by the expedient means of transillumination of the cranial vault. In the case presently reported this was done postoperatively with an ordinary pen flashlight (Figs. 2 and 3). Hydro-

cephalus may also transilluminate, as does hydranencephaly. (1) This, according to some observers, obviates transillumination as a pathognomonic feature of hydranencephaly. The hydrocephalic cranium will transilluminate best when it has reached an advanced stage, that is, when both cerebral atrophy and cranial enlargement are approaching a maximum. Transillumination is of more value in the subtle case of cranial enlargement. The hydranencephalic with early head enlargement may have a great paucity of cerebral tissue and hence transilluminate well, while the hydrocephalic with early enlargement may still have a good deal of cortical tissue present and therefore transillumination will not be as manifest. Olive and DuShane[2] pictorially present some cases of hydranencephaly which reveal the light coming through the pupils of the eyes. If hydrocephaly were to reveal the same degree of transillumination there would be a great deal of cranial enlargement and cranial atrophy. The value of transillumination is then greatest when applied early in the course of cranial enlargement. Ford[1] reports a case of hydranencephaly without enlargement of the head in a newborn infant. The baby behaved normally at first and then died with a 94° F. temperature on the fourth day of life. Had the baby lived, enlargement of the head might have become evident. Very likely the diagnosis could have been established ante mortem if transillumination were used as part of the newborn examination. Post-mortem examination revealed the cortex to be composed merely of thin membrane of a vascular nature with glial cells predominating. DuShane emphasizes that the diagnosis be made during life. The newborn child for the first few months of life will exist at a decorticate level. The infant with hydranencephaly may exist in a condition which is difficult to differentiate from that of the normal newborn infant for a period of time. Some of these babies may even be recommended for adoption. (2) Transillumination will aid in pointing up the presence of hydranencephaly early and will help evaluate the problem of the subtle enlargement of the head; for if enlargement is not great and transillumination is marked, a paucity of cerebral tissue can be suspected, with its consequent prognosis.

Fig. 2.—Ante-mortem transillumination with pen flashlight.

Fig. 3.—Ante-mortem transillumination with flashlight.

SUMMARY

A case of hydranencephaly is presented. Ante-mortem transillumination and post-mortem illustrations of the cranial vault are also presented. Early use of transillumination of the cranium as an added diagnostic measure has been re-emphasized. In the case presented transillumination was carried out after surgery and prior to death.

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A North Carolina Beauty

May be seen at Mr. William Pinchon's in second street, a MALE CHILD, from North-Carolina, of the most extraordinary size ever known of the same age. His body and limbs are much larger than any mans of the middle size. Nothing in the human shape can exceed him in point of beauty in every respect—he is healthy, amazingly strong and active, and has frequently lifted men who have weighed from 150 to 160 pounds. He is now six years old and weighs 145 pounds. He has given the greatest satisfaction to all who have seen him, and is thought to be the greatest phenomenon of the present age.

FROM A PHILADELPHIA NEWSPAPER, May, 1787.

SUPRARENAL TUMOR (CUSHING'S SYNDROME)

M. G. Peterman, M.D.
Milwaukee, Wis.

THE case of this patient is reported because he had bilateral suprarenal tumors, but he did not conform completely to the clinical picture as described by Albright. The obesity was marked and developed rapidly, but was definitely associated with an excessively abnormal appetite; the fat accumulation involved not only the face, neck, trunk, and abdomen, but also the extremities. The muscular weakness was not marked; the osteoporosis was of moderate degree. In contradistinction to impotency, this boy had precocious puberty and virilism.

Tumors of the suprarenal gland produce a definite well-known entity conveniently called Cushing's syndrome. The literature is replete with case reports of this condition and exhaustive studies have been made. In Albright's second paper on the subject he specified certain clinical manifestations and states that "the diagnosis would be questionable in any case which did not have the first three of these manifestations. They are: (1) diabetes, which is usually mild and often only demonstrable as the responsiveness to an alimentary hyperglycemia (i.e., decreased sugar tolerance), but which is resistant to insulin; (2) muscular weakness, with a low creatinine excretion as an indication of decreased muscle mass; (3) osteoporosis, especially of the spine (not to be confused with osteitis fibrosa generalisata or with osteomalacia since the serum phosphatase level is normal rather than high), associated with hypercalcinuria early in the disease and, in many instances, with nephrolithiasis; (4) a thin, reddish (?) (transparent) skin, easy bruisability, often large purplish striae, a marked susceptibility to skin infection; (5) impotence in men and amenorrhea in women; (6) mild to moderate obesity, with a tendency for the fat to be deposited in the neck and face (mostly in the face) and to spare the extremities; (7) mild hirsutism without other evidence of virilism (clitoris not enlarged, thyroid cartilage and voice normal in females), usually but not always associated with a slight to moderate elevation in the urinary excretion of the 17-ketosteroids; (8) mild erythrocytosis (red count circa 5.8 M) without increased blood volume; (9) hypertension and arteriosclerosis often accompanied by coronary heart disease and vascular disease of the kidneys."[1] This paper presents a thorough study of the problem. Among the other papers there were thirty-three well-studied cases presented by Knowlton[2] in 1953. The electrolyte disturbances in Cushing's syndrome were reviewed by Sprague and Power[3] in 1953. Subtotal adrenalectomy for Cushing's syndrome was re-

viewed in detail by Priestly and associates[4] in 1951. Twenty-nine cases were presented. Other pertinent reports concerning the syndrome are listed.[5]

CASE REPORT

A 10-year-old boy was first seen on Aug. 23, 1951. He was born Sept. 3, 1941, a full-term infant of the first pregnancy, with a normal labor and

Fig. 1.

delivery and a birth weight of 6 pounds 8 ounces. The physical and mental development were considered to be normal. The boy had chicken pox in 1947 and a mild case of measles in 1948. The tonsils and adenoids were removed when he was 2 years of age. In the past two years the boy had been gaining weight steadily at the rate of about 5 pounds a month. Previous to this he was considered to be nervous and underweight. He had grown in two years from 60 to 168 pounds. The secondary sex characters had been noted to develop. On examination, this boy weighed 154 pounds and measured 52 in. in height (Fig. 1). Nutrition was fair; mental response, excellent. The blood pressure was 120/100. The left upper central incisor was missing. The tonsils were out clean. The genitals were normal in size but the pubic hair showed a female type of distribution. The urine was negative; the blood count was normal. The blood Wassermann was negative; sedimentation rate was normal. He was obviously obese but most of his excess weight was in the trunk, with a "buffalo hump" over his upper thoracic spine. His face was round with red cheeks. There were striae in the axillae and in the groins. The extremities were thin and slightly weak. He was referred to Milwaukee Children's Hospital on Aug. 25, 1951, where the following observations were made: X-rays of the kidneys, ureters, and bladder were negative or normal. An intravenous pyelogram was negative. X-rays of the long bones showed a moderate degree of osteoporosis. X-rays of the wrist showed a bone age of 10 years. Examination of the fundi and of the visual fields showed no abnormalities. The basal metabolic rate was –24. Blood pressure in the hospital ranged from 145/80 to 180/130. On Sept. 11, 1951, the epinephrine tolerance test showed a fasting blood sugar level of 139.5; after the injection of 4 minims of 1 to 1,000 crystalline epinephrine: in 15 minutes 154 mg., in 30 minutes 176 mg. Three days later, a careful check on the blood pressure showed the following: supine—right arm 190/144, left arm 184/130; sitting up—right arm 174/136, left arm 180/132; standing—right arm 174/132, left arm 182/146. September 10 determination of the steroids by Dr. H. L. Mason of the Mayo Clinic was reported as follows: 17-ketosteroids 6.4 mg. in twenty-four hours, cor-

ticosteroids 0.127 mg. in twenty-four hours. The serum cholesterol was 337 mg. The alkali reserve was 58.9 vol. per cent; sodium chloride 561 mg.; sodium 150 meq.; phosphorus 6.2 meq. The glucose tolerance test showed a fasting level of 122 mg. (capillary blood). After 100 Gm. of glucose the following changes were noted: one-half hour, 187 mg.; one hour, 210 mg.; two hours, 167 mg.; three hours, 156 mg.; four hours, 165 mg. Ten units of insulin was then injected. In one-half hour the blood sugar was 154 mg. The Thorn test on Sept. 7, 1951, showed the following reaction: 225 mg. of ACTH injected intravenously at 9:00 A.M., 44 eosinophils; at 12:00 noon, 31 eosinophils. On September 11, before 9:00 A.M., 78 eosinophils; in one-half hour, 34 eosinophils. A diagnosis of Cushing's syndrome or adenoma of the suprarenals was made. Dr. W. W. Engstrom saw this boy in consultation Sept. 8, 1951, and concurred in the diagnosis. Dr. Philip Seefeld saw the boy on September 11 and also concurred in the diagnosis. On September 11 the epinephrine tolerance showed the following: before the injection, blood sugar level 139.5 mg.; after the injection of 4 minims of 1 to 1,000 crystalline epinephrine, in 15 minutes the sugar was 154 mg.; 30 minutes, 176 mg. On September 13, Dr. Philip Seefeld did a total adrenalectomy on the left side. The adrenal measured 5 by 2.5 by 1.5 cm. It was dark red with some nodularity on the surface (Fig. 2). Cut section showed cortical adenoma 1 cm. in diameter. Microscopic examination by Dr. Gorton Ritchie showed the following: "The cortex was largely replaced by masses of large cells with round nuclei and eosinophilic granular cytoplasm. Some cells were much larger than average and contain hyperchromic nuclei with very prominent nucleoli. A few of the cells were vacuolated, the vacuoles being fine and uniform in size. Some of the tumor cells contain finely granular brownish pigment; an occasional macrophage contains clumps of yellow brownish pigment. Many groups of small cells with doubly staining nuclei were present and among these there were many pigment-containing phagocytes. No mitotic figures seen. The normal cortical cells appear somewhat crowded and greatly reduced in number but were otherwise not significantly altered. The medulla was normal in appearance. The cells of the adenoma described above

Fig. 2.

were similar to those found in the androgenic or 'X zone' in the adrenal cortex of the newborn infant. Multiple androgenic adenoma of the adrenal cortex." Postoperatively on the first day the patient was given 50 mg. of cortisone every four hours. On September 14 this was changed to every six hours, and ascorbic acid was added, 250 mg. three times a day. On September 15 the cortisone was continued every eight hours and "DOCA R" (desoxycorticosterone) was added 5 mg. daily, and sodium chloride, 1 Gm., was given every eight hours. On September 16 cortisone

was given, 50 mg. every twelve hours, and sodium chloride, 1 Gm. every twelve hours. On September 18 sodium chloride was discontinued. Cortisone was given, 25 mg. every twelve hours. On September 20 the cortisone was given 25 mg. once a day. The cortisone was discontinued four days later. On September 26, a twenty-four-hour urine specimen was sent to Dr. H. L. Mason at the Mayo Clinic, who reported the following determinations: 17-ketosteroids, 1.8 mg.; corticosteroids, 1.01 mg. The following day the glucose tolerance test on capillary blood showed the following: fasting, 135 mg.; after 100 grams of glucose given by mouth, in one-half hour the blood sugar was 187 mg.; in one hour, 171 mg.; two hours, 165 mg.; three hours, 141 mg. The boy was discharged from the hospital Sept. 29, 1951. He was seen at my office Nov. 2, 1951, at which time he weighed 146 pounds and measured 52 inches. He had a voracious appetite and was eating an exceptionally large amount of food. Blood pressure was 142/110. It was impossible for the parents to control the boy's intake of food. At that time, two months after surgery, x-ray treatment to the pituitary glands was advised. Six treatments were given in three weeks. There was a complete loss of hair over the temporal areas on both sides. By December 29 the weight had dropped to 138½ pounds. The blood pressure was 118/80; the skin seemed to be much better, but the pseudogynecomastia was increased and the breasts were rather pendulous. On Jan. 10, 1952, the 17-ketosteroids were 1.5 mg. By February 8 the weight had further decreased to 126 pounds; the height was 52¼ inches. The blood pressure, however, was increasing, 132/80. The acne was much improved; there were no striae. The pubic hair had become sparse. By April 11, 1952, the weight was 121¾ pounds, the height 52¾ inches. Blood pressure was 122/70. The pubic hair was growing up in the midline. By July 2, 1952, the weight was 127½ pounds, height 53½ inches. There was no acne. The breasts were larger. There was no more hyperkeratosis on the lateral border of the arms. There were no striae. The blood pressure was 134/82. The 17-ketosteroids were 3.5 mg. The patient was readmitted to the Milwaukee Children's Hospital Oct. 20, 1952, and three days later Dr. Seefeld did a subtotal removal of the right suprarenal gland. The pathologic findings were the same as those in the left suprarenal gland. Immediately after operation the blood pressure was 120/48, pulse 100. At 6:30 P.M. the blood pressure was 114/80. Following this the daily blood pressures ranged from 130/70 to 114/70. He was given cortisone immediately after operation in the following dosage: preoperative, 25 mg. at 12:00 noon, at 6:00 P.M., and 10:00 P.M. He was given 100 mg. intramuscularly just before operation and then 50 mg. by mouth every six hours. After surgery he was given 100 mg. intramuscularly at 6:00 P.M. and 50 mg. intramuscularly every four hours. The following day the dosage was increased to 50 mg. cortisone every six hours. On October 25 this was changed to every eight hours. On October 27 the intramuscular injections were discontinued and he was given 50 mg. of cortisone orally every 8 hours; October 29, 25 mg. every eight hours; October 30, 12.5 mg. every eight hours; November 1, 10 mg. every eight hours; November 4, 5 mg. every eight hours; November 5, 5 mg. every twelve hours; November 8, 10 mg. every eight hours. November 9 he was discharged from the hospital on 10 mg. every eight hours. By November 20 the weight was 137 pounds, height 53¼ inches. Blood pressure was 120/70. At that time the boy was put on cortisone, 12.5 mg. every twelve hours. By December 20, 1952, the weight was 127¾ pounds, the height 53½ inches. Blood pressure 120/70. The weight by January 6 was 125¾ pounds and the height 54 inches. Blood pressure

115/60. The cortisone was given, 25 mg. in the morning and 12.5 mg. in the evening. On January 20 the weight and height were the same. The boy had regained his strength and his appetite was good. Blood pressure 120/80. The cortisone was reduced to 12.5 mg. twice a day. He was then given some Dexedrine ("Spansules R") 0.01 Gm. every morning. By Feb. 20, 1953, the weight was 116½ pounds, height 54⅛ inches. There were no complaints and the appetite was curbed; however, the boy had become a behavior problem in school. Following his first operation the school work had deteriorated and the behavior problem increased. At this time he developed an unusual interest in sexual activity and needed to be watched closely. He seemed to have erections but they were not of long duration. The cortisone was reduced to 12.5 mg. morning only. After one week the boy complained of severe ringing in the ears and he had weak spells about twice a day, one fainting spell on March 26. Blood pressure was 100/60. The face appeared much thinner, and the mother was advised to give cortisone, 12.5 mg., twice a day if necessary (Fig. 3). On April 1, 1952, an electroencephalogram was done and a satisfactory record was obtained. This showed a basic frequency of 8 per second. During light sleep there were a number of bursts of 14 and 6 per second positive spikes in the temporal lobe leads. There was random spiking in the occipital region throughout the record. There was a big build-up on hyperventilation, with larval bursts of spike wave activity. Phenacemide (Phenurone), 0.25 Gm., was given every twelve hours. On April 15, 1953, the mother reported that the school work was still poor and deteriorating rapidly. On a dosage of 12.5 mg. cortisone the boy was sleepy; when he was given 12.5 mg. twice a day he became much more active if

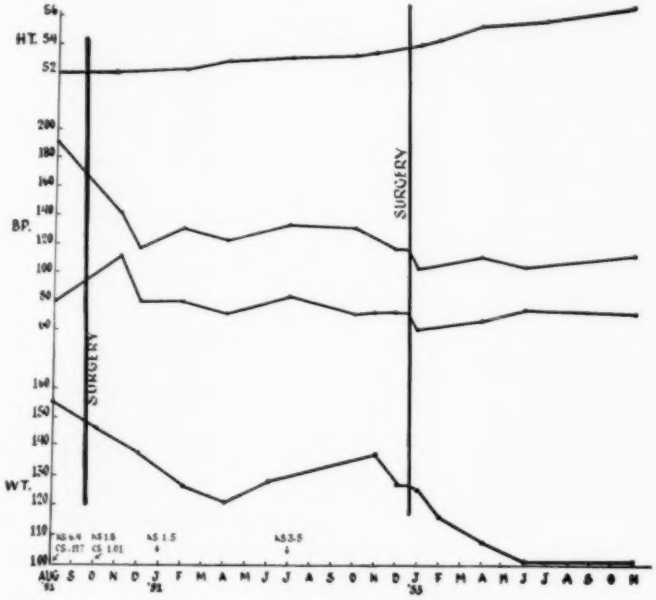

Fig. 3.

not drowsy, but was a very disturbing element in school. He was then put on cortisone, 12.5 mg. in the morning and 6.25 mg. in the evening. The phenacemide was increased to 0.25 Gm. every eight hours. The weight was down to 106½ pounds, height 55 inches. Blood pressure was 106/68. There were loose folds of skin and the breasts were rather pendulous. There were no striae. Sedimentation rate was normal; blood count was normal. By May 26, 1953, the weight was 102¼, height 55 inches. There were no striae; the skin hung in loose folds. The breasts and nipples were large. The blood count was normal. Blood pressure was 102/70. The behavior was still bad; therefore the Phenurone was discontinued. The cortisone was continued at 12.5 Gm. every twelve hours. The weight dropped to 98½ pounds Oct. 24, 1953. (Figs. 4 and 5.) There was a complaint of weakness in the afternoon and the cortisone was increased to 25 mg. in the morning and 12.5 Gm. in the evening. By Sept. 1, 1955, the boy returned, weighing 128 pounds; his height was 58½ inches. He had been well and wanted to play football on the school team. He had become careless about his diet and indifferent to his weight.

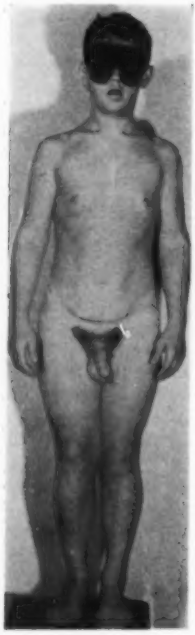

Fig. 4.

Fig. 5.

DISCUSSION

This patient made a rapid weight gain of five pounds per month and an increase from 60 to 168 pounds at 10 years of age when his height was fifty-two inches. He had a typical round ("moon") face, a fat neck, well-developed pendulous breasts, but also marked fat deposits on the extremities, as may be seen in the photograph. The basal metabolism was low; the blood pressure was high until after operation, when it dropped

to normal. After the first operation and removal of the left suprarenal tumor an attempt was made to control the blood pressure and symptoms by irradiation over the pituitary gland. The blood pressure dropped to 118/80, but the pseudogynecomastia increased considerably. The blood pressure then increased to 134/82 and a subtotal removal of the right suprarenal gland was done. Following this, the blood pressure gradually decreased to 115/60. However, the behavior problem had become serious and eventually the boy became a disturbing element in school. With cooperation it was possible to keep the weight and blood pressure near normal on small doses of cortisone (2.5 mg. twice a day). However, when the boy moved out of the city and cooperation and control were lost, the weight increased from 98½ pounds in October, 1953, to 128 pounds in September, 1955.

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ERYTHEMA ANNULARE CENTRIFUGUM (DARIER) IN A NEWBORN INFANT

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ALTHOUGH erythema annulare centrifugum (Darier) has been reported innumerable times in dermatologic literature, nowhere have the authors been able to find any report of this condition arising at, or shortly after, birth. In a related (or perhaps identical) disorder, namely, erythema figuratum perstans, Wende,[1] in 1908, stated: ". . . . there is no special sex or age predisposition. The disease asserts itself in earliest childhood as well as later in life. In rare instances it begins at birth and may be regarded as congenital." There are, however, no specific references made to any infants who were found to have this condition at birth, although he does discuss fifteen cases of erythema figuratum perstans in patients 5 years of age and older. In view of this rather oblique fact, we deem it important enough to report the case of an infant who developed the classical objective findings and fulfills all the criteria of erythema annulare centrifugum (Darier) before he was 24 hours old. By the "classical objective findings" I refer to Darier's original description of his "Classical" case. In 1916 Darier[2] described an eruption which consisted of "large rings with elevated borders in festoons or ares, protuberant and firm to the touch, which covered large areas of the trunk. They were pink and bore a slight scale. The lesions grew eccentrically and the outlines of the lesions changed accordingly so rapidly that at the end of eight or ten days the original lesion was entirely transformed. In turn, this design broke up, disappeared and was replaced with new elements of the same type. Attack followed attack. . . ."

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CASE REPORT

T. K., a white male, was born on Dec. 12, 1955. The patient was full term and the period of gestation and delivery were uneventful. No eruption of any kind was noted at birth. Within the first twenty-four hours, however, the patient was noted to have developed small "hives" over the trunk which soon began to grow, leaving clearings in the centers of each. The borders grew centrifugally and were indurated, red, raised, and had a rubbery feel. There was very little scaling. These borders soon broke up and finally assumed gyrate, scalloped, and arciform arrangements. These occurred over the entire body, with the exception of the palms and soles. They were occasionally very marked over the face and scalp. With the exception of two days, the patient has not been without these lesions, and new lesions have formed continuously up to the time of this writing (July 1, 1956), the patient now being in his seventh month. The two days when the patient was entirely free of lesions

began on May 13, 1956, eighteen hours after he had been given his first injection of diphtheria-whooping cough-tetanus toxoid. Forty-eight hours later the "hives" began again and the entire process repeated itself. It is interesting to note that on June 12, 1956, when the patient was given his "booster" injection of diphtheria-whooping cough-tetanus toxoid, none of the lesions disappeared. So far as

Fig. 1.—T. K., aged 4 months. Annular margins of lesions can be clearly noted.

can be determined there are no subjective symptoms whatsoever. Permission for biopsy was refused.

A thorough history of the patient's mother, father, and siblings revealed no noteworthy information. The mother has had recurrent backaches for the past fifteen years and takes an occasional (once every two weeks) aspirin-Phenacetin-codeine tablet.

SUMMARY AND COMMENT

A case of erythema annulare centrifugum (Darier) in a newborn infant is described. This is perhaps the first such case reported in a newborn infant. Following the first injection of diphtheria-whooping cough-tetanus toxoid, the lesions disappeared completely for a period of forty-eight hours but promptly recurred. Reference is made to Darier's original description. The etiological factors still remain a mystery.

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CLINITEST-PRODUCED ESOPHAGEAL STRICTURE

Report of Two Cases

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ESOPHAGEAL stricture secondary to lye ingestion has been widely reported in the literature. In the past three months at Brooke Army Hospital we have seen two cases of esophageal stricture due to ingestion of Clinitest tablets.

Clinitest, as stated on the label, consists of copper sulfate, caustic soda, sodium bicarbonate, and citric acid. Caustic soda is usually marketed as dry sodium hydroxide, which liberates a marked amount of heat when put into aqueous solution. This heat of hydration, plus the caustic action of the sodium hydroxide on the esophagus, is apparently sufficient to cause a thermal type of burn in addition to a chemical burn with resultant scarring and stricture formation.

Since Clinitest tablets are used more frequently and the dangers of ingestion are not widely known, the following two cases of nondiabetic children ingesting tablets are reported.

CASE REPORTS

Case 1.—A 3-year-old white male, whose parents had just moved into a house previously occupied by a diabetic, went into the yard to play. He returned to the house coughing and choking, with a bottle of Clinitest tablets in his hand. He was immediately given water and taken to a local hospital where gastric lavage was performed as prophylactic therapy for copper sulfate ingestion. During the next few days the parents noted a decrease in appetite and three weeks later he began vomiting food. After this had persisted for several days he was again taken to the hospital and treated symptomatically. Six weeks after ingestion the patient refused to drink even clear liquids and a weight loss of over six pounds was noted by the parents.

On admission to our hospital he weighed 34½ pounds. Physical examination revealed a well-developed, malnourished child with evidence of recent weight loss. He was lethargic, but his skin was clear, with fair turgor, although there was scant subcutaneous tissue. The remainder of the physical examination was within normal limits.

Following admission to the pediatric service a barium swallow was performed. This revealed an esophageal stricture at the level of the third thoracic vertebra, with only a small amount of barium going through the stenotic site. The esophagoscopist was unable to visualize the lumen demonstrated by barium swallow, but described an indurated blind pouch in the posterior wall about 5 cm. below the constriction of the cricopharyngeus at the level of the aortic arch.

Case 2.—A 23-month-old white male was given a Clinitest tablet which an elder brother had found in the medicine cabinet. The child's mother had obtained the tablets in order to test the urine of a sister to

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rule out diabetes. The patient apparently vomited part of the tablet immediately after ingestion. He was taken to a local physician who placed him on a strained food diet. However, after a week the child began to vomit occasionally immediately after eating. Three weeks later a barium swallow was reported as normal, although the film was stated to be technically unsatisfactory. Vomiting persisted, and by five weeks after ingestion the child had difficulty in swallowing even liquids. A repeat barium swallow revealed a localized constriction in the upper mid-esophagus and the child was then referred to this hospital for therapy.

Admission physical examination revealed a well-nourished, well-developed child who was 32 inches tall and weighed 23½ pounds. He was in no obvious distress and did not appear to be ill. There was no evidence of recent weight loss, and the remainder of the physical examination was within normal limits.

Barium swallow revealed a constriction of the esophagus in the region of the aortic arch, 4 mm. wide and 3 mm. in length. There was free flow of barium with good peristalsis, but there was a slight proximal dilatation at the site of the constriction.

DISCUSSION

Review of the medical literature has revealed no previous reports of Clinitest ingestion in childhood. Communication with the manufacturers of Clinitest indicates that they have had no previous reports of this type.

Owens[1] reviewed a series of 131 cases of chemical burns of the esophagus at the Los Angeles County Hospital during the period 1948 to 1952. He found that sixty-four, or 48.8 per

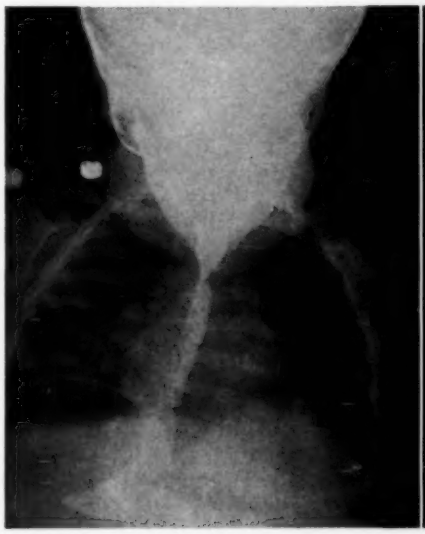

Fig. 1.

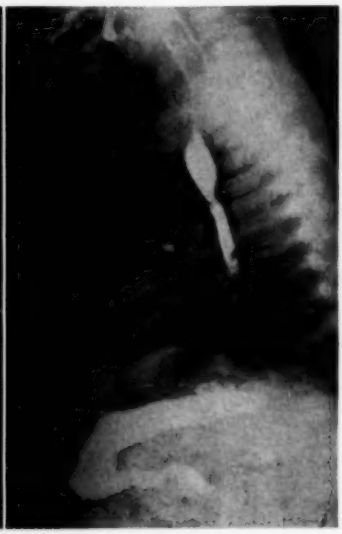

Fig. 2.

Fig. 1.—Anteroposterior view demonstrating stricture site at level of third thoracic vertebra, Case 2.

Fig. 2.—Lateral view demonstrating stricture site at level of third thoracic vertebra, Case 2.

cent, were due to lye ingestion, twenty-nine cases, or 22.1 per cent, to Lysol, and eleven cases to ammonia. Of the 131 cases there were twenty cases, or 15 per cent, in which stricture formation developed. Of these twenty cases, nineteen were due to lye ingestion, the other case occurring in an adult after he had ingested Clinitest tablets. The stricture following the Clinitest tablet in this series, as in our cases, was found at a high level. The most frequent site of stricture formation in these nineteen cases was the lower third of the esophagus.

SUMMARY

The early clinical course of two children who ingested Clinitest tablets without recognition by the attending physician of the nature of the potential damage has been described. The resultant stricture formation of the esophagus six weeks after ingestion of the tablets is demonstrated. This represents an unusual type of lye ingestion with, however, expected sequelae.

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Some Early Advice on "Demand" Feeding

The business of a nurse is to suckle the child whenever it is hungry or dry, but not by any means so often as it shrieks or cries, because by this its little stomach becomes overloaded, its food cannot be digested, and by changing in the stomach, grows acid and acrid, then causes vomitings, attended with gripes in the bowels. Nurses and mothers imagine this vomiting a sign of childrens thriving well, but we may compare it to that of a full grown person, who eats and drinks so often and in such quantities, that he is obliged to vomit several times in the day. A nurse would therefore do well, to use the child to suck at certain hours in the day, and even then no more than what is necessary: she may easily perceive when it wants to be suckled,

1. From the time it has gone without suck.
2. If it fixes its eyes on the nurse, and they seem as it were to follow her whereever she goes.
3. If joy sparkles from the child's eyes, when she opens her breasts.
4. By the child sucking her finger on its being put into its mouth.

FROM THE ENGLISH EDITION (1776) OF THE SWEDISH TEXT "THE DISEASES OF CHILDREN AND THEIR REMEDIES" BY ROSEN VON ROSENSTEIN (1771).

COR TRIATRIATUM

Report of a Case With Observations on Surgery

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THE heart with three atria is a rare congenital anomaly. Cases have been reported by Barnes and Finlay,[1] and by Parsons[2]; the latter reviewed the literature and surveyed the possible causes of the condition.

The possibility of surgical treatment for this lesion was mentioned by Barnes and Finlay. The present case report indicates some of the problems of such treatment. The results of cardiac catheterization are also included.

CASE REPORT

This was the sixth child of healthy parents. The pregnancy and labor were uncomplicated, and he appeared normal at birth. In the first few weeks of life some apathy and poor appetite were noted. At the age of 4 weeks, the infant had an attack of extreme pallor and breathlessness. Consciousness was not lost; there were irregular, struggling movements of the limbs, but no true convulsion developed. This lasted about five minutes, and the infant seemed normal afterward. Examination by the local physician at this time revealed a murmur, but no other definite signs. One week later there was a similar attack. This time transient cyanosis was followed by extreme pallor. While on the way to this hospital a few days later, the infant had a similar though more severe episode. Dyspnea was more severe and persistent. He was admitted to the hospital at the age of 7 weeks.

Clinical examination revealed severe dyspnea with rib and sternal retraction. The color was gray and the expression anxious. The peripheral pulses were present, equal, and synchronous. The heart was enlarged to percussion. The apex beat, although displaced, appeared of the normal type. A generalized, harsh, systolic murmur was present over the anterior chest. The pulmonary second sound was of the usual single, infantile type. The liver was enlarged to the unbilical level; occasional fine râles were heard at the lung bases.

X-rays (Fig. 1) showed general cardiac enlargement. The lung vessels were prominent. The electrocardiogram suggested right ventricular hypertrophy. The preliminary diagnosis was of a large left-to-right shunt with early congestive cardiac failure.

Cardiac catheterization was carried out after adequate digitalization was obtained. The procedure was effected by way of the left femoral vein. Intermittent complete heart block was a complication, and because of the infant's poor condition, oxygen was given throughout the study. The catheter could be passed into an anomalous pulmonary vein which apparently entered the left subclavian vein (Fig. 2). The atrial septum was also traversed, and the catheter placed in the left atrium and ventri-

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cle. Oximeter sweeps from the left internal jugular vein through the superior vena cava and right atrium to the inferior vena cava revealed the oxygen saturations in these sites to vary between 90 and 98 per cent. The pulmonary artery was entered; this vessel had a pressure of 118/56, with a mean of 83 mm. of mercury. The oxygen saturation here and in the right ventricle was 92 per cent.

Air collection was found to be impracticable, so that cardiac output, shunts, and resistances were not calculated. Table I gives details of the catheterization findings.

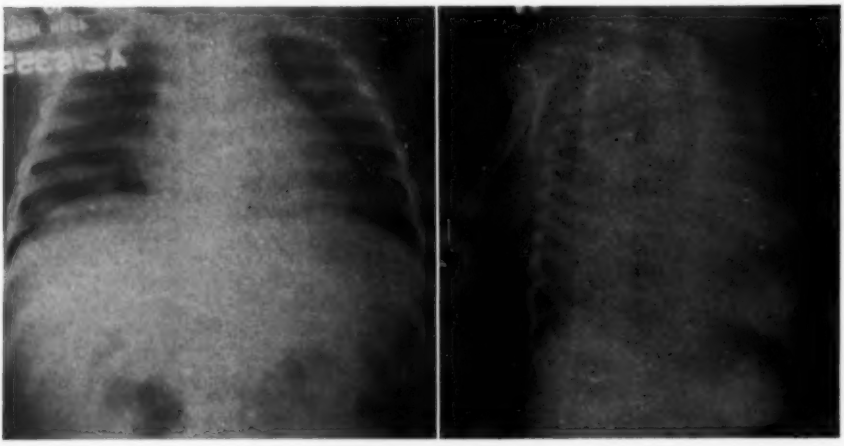

Fig. 1.—These views (posteroanterior and right oblique) show the large heart and increased pulmonary vascularity.

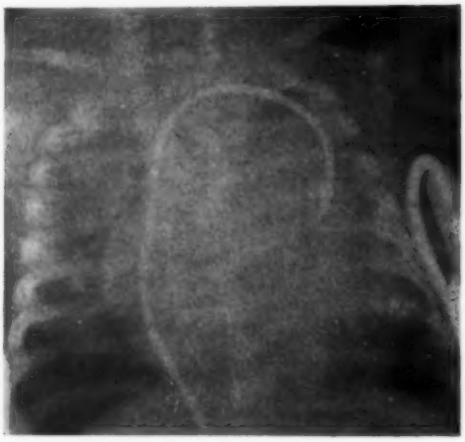

Fig. 2.—The cardiac catheter is seen entering a left superior pulmonary vein.

The conclusions from this investigation were that an anomalous pulmonary vein or veins drained into the subclavian vein or superior vena cava. The pressure gradient from right-to-left atrium without desaturation of

the latter chamber suggested that the septal defect was a nonfunctioning foramen ovale. Right ventricular and pulmonary hypertension were present. Femoral arterial saturation was 100 per cent while the infant received oxygen.

The patient's congestive failure was controlled, but his condition remained poor; it was decided therefore to attempt the surgical reposition of the transposed vein or veins.

TABLE I. RESULTS OF CARDIAC CATHETERIZATION
(Procedure carried out with continous oxygen)

CATHETER POSITION	PRESSURE (MM. MERCURY) S./D.	PRESSURE (MM. MERCURY) MEAN	O_2 CONTENT (VOL. %)
Jugular vein	--	--	12.6
Left subclavian	--	--	15.3
Superior vena cava	--	10	15.2
High right atrium	--	--	15.2
Mid-right atrium	--	10	14.0
Low right atrium	--	--	14.7
Inferior vena cava	--	10	12.7
Pulmonary vein (entering subclavian)	--	--	15.5
Left atrium	--	6.4	15.3
Left ventricle	77/5.7	--	15.5
Right ventricle	118/0	--	14.3
Pulmonary artery	118/56	83	14.3
Femoral artery	89/57	69	15.5

Operation (W. P. Y.).—Thoracotomy disclosed a persistent left superior vena cava which received an unknown number of pulmonary veins. It drained into the right atrium by way of a right superior vena cava. The left ventricle was small, and the left atrium not unduly distended. Its appendage was small. As the course of all of the lung veins could not be determined, the anomalous vena cava was cautiously occluded for ten minutes. The left ventricle and proximal pulmonary veins appeared to increase in size; the infant's condition remained satisfactory. It was therefore assumed that some communication, however small, existed between the pulmonary veins and the left atrium. The anomalous channel was dissected free, divided, and anastomosed to the left atrium at the site of its amputated appendage. Due to the fragility of the venous trunk, this maneuver occupied twenty minutes. During this time, the electrocardiogram showed marked elevation of the S-T segments with "T"-wave inversion. These changes reversed on opening the anastomosis. The infant's condition improved, and the chest was closed in the normal fashion with pleural drainage and suction.

Postoperative Course.—The patient's condition improved remarkably. The grayish pallor disappeared and dyspnea was less. This happy state continued for forty-eight hours, when the infant again had an episode of pallor and breathlessness similar to that seen before surgery. A few hours later focal fits were seen, and the infant died three days following the operation. Clinically, the cause of death appeared to be left ventricular failure.

Autopsy.—The right atrium and ventricle were enlarged, the left ventricle was small. The systemic venous return showed a surgically interrupted persistent left superior vena cava which entered the right superior vena cava by way of the innominate vein.

The atrial septum had a defect 6 by 3.5 mm. at the site of the foramen ovale; through this a probe could be introduced into the left ventricle.

Dissection of the left atrium showed this chamber to be bisected by a membrane, with a central foramen 2 mm. in diameter. The lower chamber, from which the atrial appendage had sprung, communicated directly with the mitral valve and left ventricle. The superiomedial chamber was associated with the right atrium by the foramen already described. The anastomosis was patent and apparently had functioned. Dissection revealed connections to the anomalous vena cava and third atrium as shown in Fig. 3 with its explanatory diagram.

Microscopy of the heart showed some endocardial thickening. The

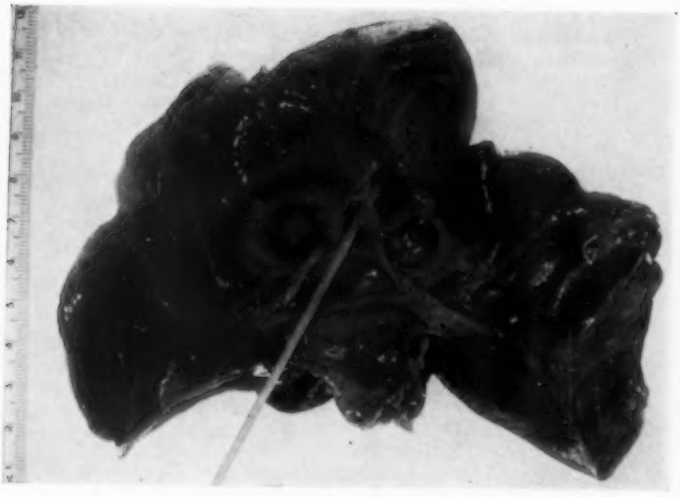

Fig. 3.—The membrane with its central foramen subdivided the left atrium. The key to the plate details the anatomy.

lung sections showed mature thrombi in some of the vessels; there was widespread arteriolar thickening. This finding has been reported by Hartmann[3] in another case of this condition.

DISCUSSION

This is a case of cor triatriatum with its usual associated anomaly of the pulmonary venous return. Clinically, the patient presented with episodes of acute dyspnea and pallor of the type associated with starvation of the systemic and coronary circulation. This may occur, for example, in lesions of the aortic valves. A diagnosis of anomaly of the lung veins was made at cardiac catheterization, and operative repair was attempted.

Although the presence of a dividing membrane was not found until autopsy, the existence of a constriction between the pulmonary veins and left atrium was postulated. The corrective method used was rational insofar as the pulmonary venous blood was delivered directly to the mitral orifice. The immediate result was good, but the left ventricle, already small from "disuse" atrophy, was unable to take the increased mitral flow. The situation is somewhat analogous to that found in fibroelastosis of the mitral valve,[4] where increase in mitral flow cannot always be expelled by the left ventricle. Repair of the small atrial septal defect might further have increased the mitral flow and, consequently, the left ventricular load.

The course of the circulation gave a large left-to-right shunt; the blood from the normally situated pulmonary veins had difficulty in entering the mitral orifice and tended to be diverted to the right atrium by way of the true septal defect as well as by the left superior vena cava.

If the presence of the interpolated membrane in the left atrium had been known at the time of the surgery, direct attack might have been possible. Open-heart surgery with hypothermia or extracorporeal circulation would have been necessary, as the atrial appendage was much too small for digitally guided instrumentation. However, the anastomosis delivered blood from the pulmonary veins to that portion of the left atrium adjacent to the mitral valve. Blood within the thin-walled persistent left superior vena cava could be easily seen to flow from the pulmonary veins to the innominate vein originally and into the atrium after this vessel had been removed from the innominate vein and anastomosed to the atrium. In any event, the crux of the problem is the ability of the left ventricle to increase its output. This cannot be discovered except by operation. The presence of pulmonary hypertension is an added hazard.

The etiology of the condition has been considered by Parsons,[2] who cast doubt upon Hagenauer's[5] theory that the condition was due to an abnormal junction of the pulmonary vein stem and the primitive heart. Borst's[6] theory also does not explain all the cases reviewed. Parson's[2] final opinion is that there is a primary disturbance of organization at the second month of development.

The present case seems to be unique in its association of a persistent left superior vena cava as the route to

the right atrium of the anomalous veins. No other report of cardiac catheterization or of surgery in such a case has been found in the literature. The case probably closely parallels that of Stöber[7]; in this instance, however, the anomalous veins drained directly into the right atrium.

SUMMARY

A case of cor triatriatum is reported. The results of cardiac catheterization and pulmonary venous reposition are described. The possibilities of surgical repair and the dangers of left ventricular failure are discussed.

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Clinical Pathological Conference

CHILDREN'S MEDICAL CENTER
BOSTON, MASS.

SIDNEY FARBER, EDITOR
JOHN M. CRAIG, ASSISTANT EDITOR

CLINICAL HISTORY

THIS was the first Children's Medical Center admission of this 3-year-old white female from Kenya who entered because of hepatosplenomegaly, inanition, and fever.

The patient was quite well until six months before admission when, while living in Kenya Colony, Africa, she developed a series of boils and styes, which responded to penicillin. A few weeks later, she developed fever and lethargy. She was given two full antimalarial courses of chloroquine without effect and, because of hepatosplenomegaly, was referred to a hospital in Kenya for further investigation.

On admission there she was noted to have a temperature between 102° and 103° F., a distended abdomen, and hepatosplenomegaly. Because of negative investigations, she was put on quinine, later Nivaquine, emetine, and Chloromycetin for therapeutic trial against malaria and amebiasis. None of these drugs were of benefit. A laparotomy was performed two weeks after admission. The liver was found to be enlarged, with a surface dotted with small, yellow, pinhead abscesses. Sections of the liver showed what was thought to be tuberculosis and she was started on a course of isoniazid 100 mg. and streptomycin 300 mg. daily. On this therapy she seemed to improve but her liver and spleen remained enlarged. She ran a total leukocyte count of 5,000 with a normal differential. A twenty-four-hour urine and a liver biopsy culture for tuberculosis were negative after six weeks.

The past history revealed that the patient was born in Maine but moved to Africa at the age of 10 months. She lived in the mountainous areas of Kenya. She is known to have been a dirt eater in Africa and to have ingested unpasteurized, but boiled, milk.

The patient had a "pyloric tumor" operated upon at age 6 weeks with a good result. There were no members of her family ill with similar symptoms at any time. Two brothers, aged 4 and 2 years, are well except that the older had encephalitis of unknown type in Africa. There was no known direct contact with any animals in Africa.

The physical examination revealed a temperature of 102° F., pulse 120 per minute, respirations 22 per minute, and blood pressure 122/85 mm. Hg. She was an emaciated, chronically ill child weighing 21 pounds.

Her abdomen was large and distended and there was marked loss of subcutaneous tissue. There was no significant lymphadenopathy. The eye grounds were negative. On the right buccal mucosa there was an irregular, white ulcerated area. In the middle of the tongue there was a 0.5 cm. circumscribed, yellowish, raised lesion. On the tonsils there were four to six raised, round, whitish globules measuring about 0.5 cm. in diameter. The chest was entirely clear. A grade II to III blowing systolic murmur was heard all over the precordium. The abdomen was large and tense, measuring 50.5 cm. in circumference at the umbilicus. The liver was 4 cm. below the costal margin, with a sharp edge, and was stony hard. The spleen tip was palpable 2 cm. below the costal margin. There was a questionable fluid wave and shifting dullness, and questionable early clubbing of the fingers. The remainder of the physical examination was negative.

Laboratory examination revealed a negative urine, a peripheral leukocyte count of 6,000 with 60 per cent polymorphonuclear cells, 31 per cent lymphocytes, and 9 per cent monocytes. The hemoglobin was 10 grams per cent. The tuberculin skin reactions were negative at 1:1,000 and 1:100. The histoplasmosis and blastomycosis skin tests were negative. Nose and throat culture grew rare pneumococci. The stool culture was negative for pathogens. No ova or parasites were seen and the guaiac reaction was negative. The liver functions were: thymol turbidity, 6 units; thymol flocculation, 2 to 3 plus; cephalin flocculation, negative. The total serum bilirubin was 0.9 mg. per cent. The chest roentgenogram was clear, and the skull and long bones negative except for osteoporosis. The serum nonprotein nitrogen level was 27 to 36 mg. per cent initially, and 44 mg. per cent terminally. The serum cholesterol was 198 mg. per cent. Two zinc flotation examinations of the stools revealed no ova or parasites. Later smear of stools revealed organisms similar to those seen in the liver. The total serum protein was 2.90 grams per cent; albumin, 2.01 grams per cent; globulin, 0.90 gram per cent.

Hospital Course.—The patient's liver biopsy sections were reviewed by the pathological department and, on restaining, granulomatous lesions were seen in which there were giant cells and large mononuclear cells containing numerous small encapsulated organisms. Smears were made from a bone marrow biopsy, from the tonsillar lesions and from the buffy coat and, in all of these preparations, organisms similar to those seen in the liver biopsy were found in abundance. All of these areas were cultured, but no immediate growth was obtained on NNN media or Sabouraud's agar. Because of gradual enlargement in the abdominal circumference, a paracentesis was performed and 750 c.c. of high protein fluid removed. A smear of this fluid showed cells containing the same organisms. Because of failure to establish a diagnosis by culture, it was decided to start the child on a course of pentavalent antimony. Accordingly, on her twelfth hospital day intravenous stibamine glucoside was started and given for two days, 25 mg. daily. Meanwhile histoplasmosis and a blastomycosis complement fixation were reported negative from the Georgia Communicable Disease Center and from the Army Medical

School in Washington, D. C. On her fifteenth hospital day, she was started on a course of 2-OH stilbamidine, 30 mg. daily, intravenously. This was given two days in succession, until intravenous nystatin became available on her sixteenth hospital day. She was given this drug from her sixteenth to her twenty-second hospital day. She received it seven days in all, starting at 30,000 units and working up to 75,000 units in single daily intravenous infusions. Just prior to the use of nystatin the patient became clinically jaundiced and liver functions showed one-minute serum bilirubin of 4.1 mg. per cent; a total serum bilirubin of 4.2 mg. per cent; cephalin flocculation, 2 plus; thymol flocculation, 2 plus; and thymol turbidity, 6 units. This was interpreted as a result of her long-standing liver disease rather than as a toxic effect of any of her drugs. On her nineteenth hospital day, she became exceedingly lethargic and the blood chemistries showed a serum protein of 2.9 grams per cent, CO_2, 15 meq. per liter, sodium, 105 meq. per liter, and chloride, 88 meq. per liter. From then until her death on her twenty-fourth hospital day, she remained hyponatremic and hypochloremic despite the administration of intravenous electrolytes and plasma. During this time, her serum nonprotein nitrogen remained normal. On her twenty-third hospital day, nystatin was discontinued because she had become oliguric. A twenty-four-hour urine collection had a total volume of 92 c.c. with a total twenty-four-hour sodium excretion of 0.1 meq. per liter and potassium of 1.6 meq. per liter. On her twenty-fourth hospital day, she quietly died in coma.

DISCUSSION

DR. LOUIS WEINSTEIN.*—My attention is first attracted to the fact that this child came from Kenya, and this raises immediately the possibility of a variety of exotic diseases. We are told that she had no contact with animals, and that she was a dirt eater. I am not acquainted with the bacterial or fungal content of the soil of Africa, but I presume that it would contain the same tremendous mixture of living beings that would be found in this country, with the addition of a variety of parasites which would probably not be present in the soil in Boston.

The most important facts stated in the protocol are that some type of encapsulated organism was observed in the liver biopsy, and material derived from the blood, bone marrow, peritoneal fluid, the tonsils, and the tongue, as well as the intestinal contents. Cultures on the Nicolle-Novy-MacNeal and Sabouraud media yielded no bacteria, although this does not rule out the possibility that we are dealing here with some type of bacterial disease, the agent of which might not multiply in these media. It raises the strong possibility that the organism, which was observed in staining preparations but not cultivated, was a fungus, a yeast, a protozoan, or some stage of some other parasite. I think these findings are strongly suggestive that we are not dealing with a bacterial disease, and I want to focus my attention, therefore, on several possibilities related to parasitization by the other types of organisms which are mentioned.

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The possibility of tuberculosis was considered and some treatment was actually given. A negative tuberculin reaction and the negative cultures of the liver tend to rule out this disease, but not completely.

First, let us consider the possibility of protozoan infections. Malaria was suspected in this child, but could not be proved, either on the basis of the demonstration of the parasites or response to antimalarial therapy. The possibility of amebic hepatitis was also suspected, but apparently not proved because of a failure to respond to amebicides, although this does not always rule out this diagnosis. I am influenced, however, to disregard this disease because of the failure of treatment and the statement that several examinations of the stools while the child was in this hospital revealed no parasites, keeping in mind that patients with amebic hepatitis may have no demonstrable parasites in the feces.

One very important protozoan disease which must be seriously considered in this child is kala-azar. The possibility was obviously thought of by the people who treated her here, because the protocols tell us that cultures were made with NNN media on which Leishmania grow, and that antimony compounds were given. There is another reason for giving the antimony compounds which I shall mention later. Kala-azar is commonest in India and China, but has been seen in several other areas of the world; it has been observed in Africa, and interestingly enough I have been able to find reports of proved cases of this disease which were studied in Kenya. The enlarged liver and spleen, the emaciation, the normal white blood count, the anemia, the peritoneal effusion, and death about eight months after the onset of the illness are all consistent with the manifestations of kala-azar. The mode of possible infection with Leishmania in this child is no less obscure than it is in most cases of this disorder. It is not yet completely established whether the organisms are transmitted to man from dogs, which are known to harbor the parasite, or by the bite of one of several species of the sandfly, Phlebotomus. In Africa, this disease has its highest incidence in August and January; it is interesting, therefore, that this is approximately the time of the year when the patient whom we are discussing became ill. Although any type of fever may be present, very frequently the disease is characterized by a daily double intermittent fever. When this occurs, it is said to be pathognomonic of kala-azar. The only other diseases I know that may produce this type of fever are malaria, in which several broods of parasites are producing infection simultaneously, and gonococcal endocarditis. Unfortunately we do not know from this protocol whether or not the patient had this type of fever. Encapsulated organisms which were observed are consistent with the appearance of Leishmania, which distinguishes it from other microorganisms, particularly certain types of fungi. In kala-azar there is usually a peculiar blackening of the tongue, from which the disease has derived its name. In white-skinned individuals a brown pigmentation of the skin also appears; neither of these features was present in this patient. In kala-azar there is frequently thrombocytopenia and a bleeding tendency. This

patient had no evidence of bleeding. I am unaware that lesions of the type described in the mouth and on the tongue and tonsils of this patient occur during the course of kala-azar. The white blood count is characteristically at leukopenic levels in kala-azar, although it may be normal. There have been a few cases in which leukocytosis has been described. Thus, this piece of data is of no help. Further, there is marked elevation of the globulin in the plasma in kala-azar. In our patient this serum component was actually reduced. This may be due to other factors which I shall mention later. So characteristic and so common is this elevation of plasma globulin in kala-azar, even in very emaciated patients, that in the rural areas of China the diagnosis of this disease is often made solely on the basis of the formation of a precipitate when a specimen of the suspected serum is dropped in the tap water. The demonstration of tubercle-like lesions in the liver is of no help in ruling in or out the possibility of kala-azar, because these are the characteristic lesions of this disease and they have often been confused with disseminated tuberculosis, until the causative organism has been isolated. The Leishmania will grow on NNN media. The failure of the organisms to grow in this case may actually have represented absence of them, or may have been due to insufficient period of incubation before the patient died. The use of antimony also suggests that kala-azar was considered. Very frequently the administration of this drug or this type of drug results in rapid improvement. We cannot assume, however, that because this patient did not recover with antimony treatment, kala-azar can be ruled out, since in this instance there might not have been enough time for a beneficial effect to be exerted. Thus, I cannot eliminate kala-azar completely as the cause of this patient's illness.

Schistosomiasis is another disease which may be confused with kala-azar. Hepatosplenomegaly has been described in this disease and some descriptions of patients are quite similar to those with kala-azar. Incidentally, schistosomiasis has been described in the area of Africa from which this patient came. I think this diagnosis can be ruled out because of the failure to demonstrate a peripheral eosinophilia and ova in the four stool specimens, two of which were examined by the zinc flotation method.

A consideration of the other so-called parasitic diseases must be limited to those in which ova are absent in the stools; these are diseases caused by Echinococcus and trichiniasis. The clinical picture which developed in this patient is certainly not characteristic of either of these diseases.

Another parasite which is suggested by the description of the encapsulated, intracellular parasite is *Toxoplasma gondii*. It is interesting that this organism was first isolated and studied in rodents and birds in Africa, and I presume that this might direct my attention to infection of this type. Hepatosplenomegaly has been observed. There are several considerations, however, which for me rule against this disease. Age 3 is somewhat older than is usually described for an infantile type of toxoplasmosis. In practically all of the young children with this disease, neurological

manifestations have been outstanding from the very inception of the illness. Hydrocephalus and convulsions are very common. This patient had no neurological abnormalities until she reached the terminal phase of her illness. The descriptions of the adult type of toxoplasmosis, which may become clinically apparent, are so few that it is impossible to talk about a characteristic picture. Nevertheless, I don't think that this patient had this kind of infection.

I come now to a consideration of fungi or yeasts as a possible factor in the etiology of this patient's disease, and the fact that it is entirely possible that she ingested yeasts or fungi. The fact that she came from Africa may have little or no bearing on her illness. A consideration in the possibility of mycotic disease is the fact that this youngster was treated for a skin infection with penicillin. As soon as I hear this story in the case of a patient who has subsequently developed some type of disseminated illness, the possibility of superinfection by yeasts or fungi related to the administration of antibiotics enters my mind, and I admit I am quite biased in this direction. This possibility is even further emphasized for me when I come to The Children's Medical Center to discuss a case at its Clinical Pathological Conference, because, if I remember correctly, the last three cases which I have discussed here have been instances of diffuse mycosis, probably secondary to antibiotic exhibition. The organisms which have been described in the study of various areas of the body are certainly consistent in appearance with that of yeasts or fungi. The presence of encapsulated organisms in the liver, the bone marrow, the blood, and intestinal contents suggests immediately the possibility of *Histoplasma capsulatum*. However, the double envelope of many of the fungi, in fact, may give the impression of encapsulation. I think that I have learned from these discussions that it may be impossible to identify the causative organisms on purely clinical grounds. There are, however, a few features of certain types of mycotic infection which help direct our attention to specific agents, even before these are isolated and identified.

In considering the specific type of infecting agent, one of the first that came to my mind was *Coccidioides immitis*. A disseminated form of this infection may appear with a very wide variety of clinical manifestations. The organism is a spherule, which is a doubly refractile body, and contains endospores. This is not consistent with the descriptions of the appearance of the organisms which were seen in our patient. Coccidioidomycosis has a predilection for bone, skin, lungs, meninges, but any organ may be involved, except the gastrointestinal tract. The absence of bone lesions is very uncommon. In addition, as far as I have been able to ascertain, no cases of this disease have been described from Africa. This might well be the first.

The possibilities of blastomycosis and histoplasmosis were considered when this patient was in the hospital. The skin lesions, which were the initial manifestations of this child's illness, are not unlike those which have been described frequently in the early phase of the disseminated form of histoplasmosis. The lesions of the tongue, tonsils, and buccal mucosa

have also been described. Skin tests and complement fixation titrations were negative for both of these. Cultures for fungi and yeast were made on Sabouraud's medium and were negative "immediately." I may put a little reliance on this "immediately." I wonder if this suggests that they became positive later. This certainly would not be unusual. It may take organisms of this type a considerable period of time to grow out. As a matter of fact, it has been stated that it may require as long as thirty days of incubation for growth of *Histoplasma capsulatum*. If the cultures are incubated at 37° F., the growth may well be delayed, since many of these organisms grow better at room temperature. The tubercle-like lesions in the liver have also been described in diffuse mycotic disease and especially in generalized histoplasmosis. So as one puts this case together, keeping the possibility of fungus infection in mind, it has a great many features which have been described as characteristic of the generalized form of histoplasmosis, and this disease has been observed in Africa. The lesions on the tongue, the tonsils, and the buccal mucous membrane, the so-called pustules on the skin, the hepatosplenomegaly, the emaciation, the albuminuria, the questionable renal lesion, and the biopsy findings, as well as the normal white count and anemia, are frequent findings in this disease. As you must have noted, these features are the same as those which are mentioned as being characteristic of kala-azar. It has been pointed out that it may be very difficult to distinguish kala-azar from the generalized form of histoplasmosis. Examination of biopsy specimen in which organisms can be seen may not even be helpful, because it may be very difficult to distinguish Leishmania from Histoplasma until the organisms have been grown in artificial media and their morphologic characteristics identified. I am bothered somewhat by the negative skin reaction and complement fixation test for histoplasmosis, because if it were not for these negative findings, I think all of the features of this child's illness are entirely consistent with the syndromes which have been described in generalized Histoplasma infection in young children. I note that the plasma globulin was low. There is no partition of the globulin presented and this might suggest that the gamma globulin level was very low or absent in this child. If this is so, then, this might explain the failure of immunologic response to the Histoplasma infection in this child, and thus giving generalized histoplasmosis with a negative complement fixation reaction. There are a few cases of proved histoplasmosis in which the complement fixation has been negative.

In any patient in whom diffuse mycotic disease is suspected, the possibility of some underlying disease should promptly also be suspected. Thus, it is known that generalized histoplasmosis tends to occur somewhat more frequently in patients who have leukemia or lymphomas. Hepatosplenomegaly in this patient may have been due to either of these entities, but the normal blood smears more or less rule out the necessity of considering leukemia. Hodgkin's disease or lymphoma, however, cannot be ruled out on the basis of the information furnished in this protocol,

and there are several reports pointing out a frequent association between Hodgkin's disease and generalized cryptococcosis or histoplasmosis.

Apparently the physicians who treated this child were also impressed by the possibility of mycotic disease, because they treated her with nystatin, which is a fungostatic agent. That this did not produce a cure is not too surprising. In mycotic diseases of this extent, treated so late, one can expect very little, if any, beneficial effect. The use of antimony compounds should have been of some benefit if this patient had blastomycosis. Stilbamine is also quite effective.

This patient's death was characterized by increased lethargy, marked abnormalities of the plasma electrolytes which could not be repaired by the administration of electrolyte solutions or plasma, and oliguria with very low concentrations of sodium and potassium in the urine, but with a normal serum nonprotein nitrogen. This raises the question immediately of whether or not this child had a renal lesion. The rigid electrolyte disturbances may have been associated with faulty regulation of water and electrolytes, which is seen in patients who have liver or other chronic wasting diseases. Nystatin might have produced physiologic disturbances which might have accounted for the changes noted, though I am, however, not aware of any such changes having been reported. Other antibiotics such as streptomycin and neomycin are capable of producing electrolyte disturbances. The latter drug readily produces hypokalemia.

In conclusion, I would like to make the following diagnoses: one, diffuse mycotic infection; I am not willing to name the type of fungus, but this case has many of the features which have been described in disseminated histoplasmosis. I cannot rule out kala-azar completely; as I have said, even the experts may have great trouble distinguishing this disease from disseminated mycoses, especially histoplasmosis. Finally, because of the reported association of lymphomas, with diffuse mycotic disease, I would like to raise the possibility that underlying this child's infectious process may be a lymphoma, or even tuberculosis, which has been found a number of times in association with a number of diffuse mycotic diseases. I would like again to mention the possibility of superinfection with a fungus or yeast as a result of the penicillin therapy of the skin lesions which were the first manifestations of this patient's illness.

DR. SIDNEY FARBER.—Thank you very much, Dr. Weinstein. Dr. Neuhauser, would you like to speak on any part of your studies?

DR. E. B. D. NEUHAUSER.—Not mentioned in the protocol is the appearance of the gastrointestinal tract. The gas pattern itself was decidedly abnormal, but was not specific for any disease process and might represent sprue or any other disturbance.

DR. WEINSTEIN.—There were no ulcerations?

DR. NEUHAUSER.—It was not examined other than by a flat plate.

DR. WEINSTEIN.—I might just say that in a number of mycotic diseases, and particularly in histoplasmosis, ulcerations of the intestinal tract have

been described. It is often not difficult to isolate the organisms from the stool, just as in this patient.

DR. FARBER.—Is there any other information that we would like to give Dr. Weinstein at this time?

DR. ROBERT HAGGERTY.—We were disturbed by the negative chest x-ray in an attempt to justify a diagnosis of histoplasmosis.

DR. WEINSTEIN.—Many cases with generalized histoplasmosis have, as a matter of fact, a primary lesion probably in the lung, but there are a number of descriptions of generalized histoplasmosis in which, at least by roentgenogram, no pulmonary changes have been observed.

DR. CHARLES JANEWAY.—I would think the negative chest film might be explicable on the basis of the intestinal lesion. This child ate dirt and may very well have ingested the organisms and developed a primary lesion in the gastrointestinal tract, and the liver acted as a filter for a large part of the organisms. Thus, she could have had most of the pathology confined to those regions. We know that the liver is seriously involved from the clinical story. I think the electrolyte disturbances again are of a sort which we have seen in very serious disease of the liver which is not easily explainable, but I can remember two or three other patients with very advanced cirrhosis who had sodium values which were down in these very low ranges. The other thing that is of interest is the extraordinarily low serum protein values. We do not have record of anything except the ordinary albumin-globulin ratio. We do not know the amount of gamma globulin in the globulin fraction here, which normally, of course, is composed of about 40 to 50 per cent of gamma globulin and the rest is alpha globulin primarily. If the whole globulin fraction has a normal distribution, it seems to me quite likely that the child's gamma globulin level was reduced. Yet this is not the kind of A G ratio that one ordinarily sees with a specific gamma globulin disturbance, but rather what has been described in patients with idiopathic hypoproteinemia, which is probably basically a disturbance of liver function. The hypoproteinemia is perhaps due to increased destruction of proteins rather than any inability to make them or to use them. I don't think you can say much more about the protein disturbances, except that without proteinuria these are extraordinarily low protein values.

DR. FARBER.—Thank you, Dr. Janeway. May I ask Dr. Diamond a question which is not in the main body of this differential? It concerns the eating of dirt by the child, and why children do that. What is the present conception, Dr. Diamond?

DR. LOUIS K. DIAMOND.—Are you asking me as a psychiatrist or as a hematologist?

DR. FARBER.—I am calling on you as a psychiatrist, not as a hematologist.

DR. DIAMOND.—Let's see if there are any psychiatrists in the audience first, before I answer. Recently in the combined meetings that many here attended at Quebec, of the British, Canadian, and American Pediatric Societies, in the discussion of lead poisoning by the group from

Johns Hopkins Medical School, the point was made that pica was one of the chief causes of lead poisoning. Two or three of our psychiatric-minded pediatricians promptly arose to say that pica was undoubtedly another manifestation of a disturbed emotional state and therefore that this pica lead poisoning secondarily was of psychogenic origin rather than any other. The only other actual data we have on the subject is the high incidence of lead poisoning in children who have had anemia, particularly iron deficiency anemia or Mediterranean anemia of long standing. There the pica has been directly related to the level of gastric acidity, since many of these children with secondary iron deficiency anemias are on a poor diet, and those with Mediterranean anemia have a relative anacidity. Both groups will respond to histamine and alcohol testing, but will have low acid content of their gastric juice without such stimulation. Immediately after cure of the iron deficiency anemia, with return of normal gastric acidity, they lose their tendency to put foreign objects in their mouth, and a supposition has been offered that children who have poor acid secretions, from whatever cause, try to chew on foreign objects because they obtain the same gastric stimulating effect from alcohol or the condiments.

DR. FARBER.—Dr. Shwachman?

DR. HARRY SHWACHMAN.—There was one child that came to this hospital in 1935 with kala-azar, and the thing that I remember about it when I was in medical school was the tremendous spleen that patient had, and this present child did not have such a spleen. Therefore, I felt immediately that this was not a case of kala-azar, but I didn't know what it was.

DR. JANEWAY.—That information, too, fits with the idea that this organism entered by way of the gastrointestinal tract, went to the liver, and the spleen enlargement only developed as a result of portal hypertension.

DR. LOUIZ CARLOS OLIERA.—In Brazil there is also a form of fungal infection which is called South American blastomycosis. It causes lesions in the mucosa of the mouth and has almost the same symptoms as described here, but it never spares the lungs.

DR. JAY BERNSTEIN.—The sections which came from Africa were shown to numerous consultants. Dr. Thomas Weller felt that this did not represent kala-azar. We showed it also to Dr. Gustave Dammin at the Peter Bent Brigham Hospital, and Dr. Chapman Binford of the Armed Forces Institute of Pathology. Both Dr. Binford and Dr. Dammin were fairly positive that it was histoplasmosis.

At autopsy the child had extensive ulceration of the hyperplastic lymphoid follicles extending from the duodenum to the anus (Fig. 1). These involved primarily the lymphoid follicles but extended beyond that and presented only on the mucosal surface. The foci of the ulcers consisted of masses of macrophages, distending the lamina propria with ulcerations on the surface (Fig. 2). These macrophage forms were frequently multinucleate and contained myriads of periodic acid-Schiff positive organisms which varied somewhat in size (Fig. 3). The mesenteric lymph

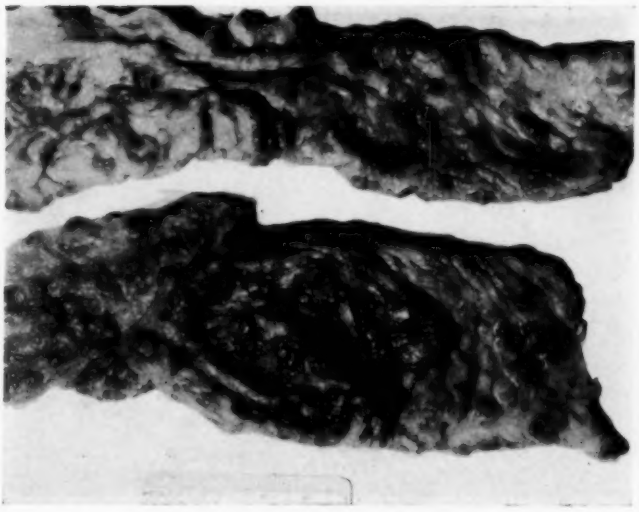

Fig. 1.—Small intestine. Many isolated and confluent ulcers are present in the mucosa.

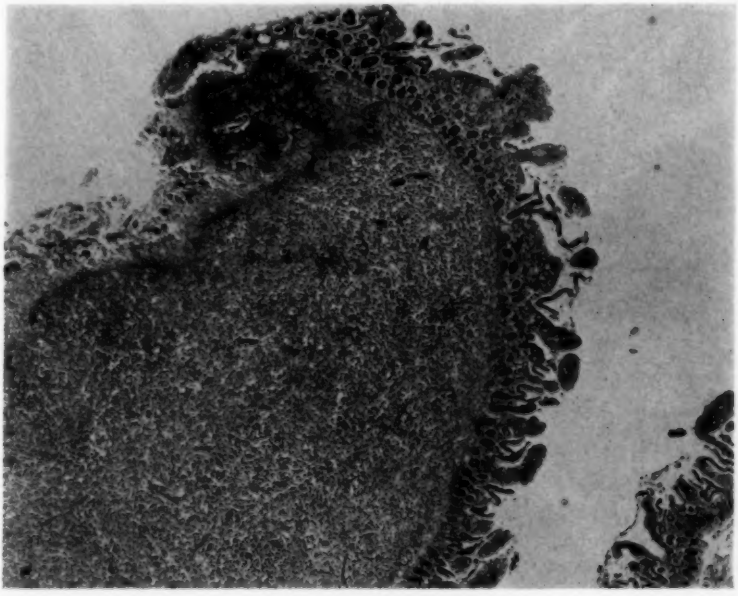

Fig. 2.—Photomicrograph, small intestine. The mucosa is elevated by the mass of macrophages in the lymphoid follicle, and is ulcerated at the left. (Hematoxylin and eosin; ×55.)

nodes were greatly enlarged, soft, and succulent, measuring up to 3.0 cm. in diameter, and these too were filled with large numbers of macrophages containing fungal forms. The liver, as might be expected, was 50 per cent overweight and had a thickened capsule and numerous scarred, depressed areas on both the free and the cut surfaces (Fig. 4). The liver had broad areas of granuloma formation, as well as necrosis (Fig. 5), and organisms could easily be demonstrated. The spleen was twice the normal value in weight, and was the seat of lymphoid and reticuloendothelial hyperplasia; only a few organisms were present and no granuloma. The adrenals contained foci of necrosis with granulomas and organisms. The lungs had only a focal bronchopneumonia; occasional macrophages within the alveoli contained organisms, but no granuloma or focus, suggesting that a primary lesion could be found.

Histoplasma organisms were also identified in the tongue, pharynx, larynx, thymus, peritoneum, and meninges. The renal tubules contained hyaline amphophillic casts and in these areas the tubules were atrophic and dilated. We believe these changes antedated the child's terminal illness or the chemotherapeutic agents administered.

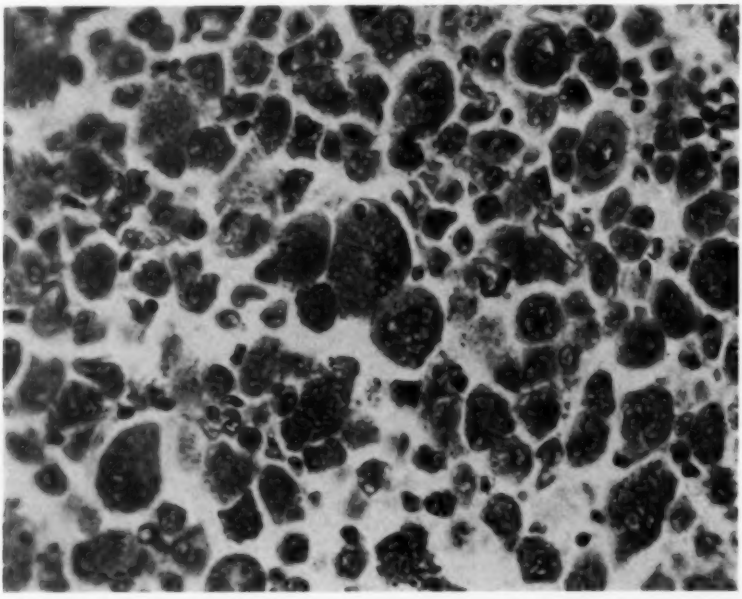

Fig. 3.—Photomicrograph, small intestine. A high-power view of the frequent multinucleate macrophages containing one to many encapsulated organisms. (McManus' periodic acid-Schiff stain; ×550.)

DR. FARBER.—Dr. Foley, would you say a word about the isolation and identification of the organism?

DR. GEORGE E. FOLEY.—We isolated both from pre-mortem samples of

Fig. 4.—Liver. The cut surface of the enlarged liver reveals the broad, depressed perivascular scars.

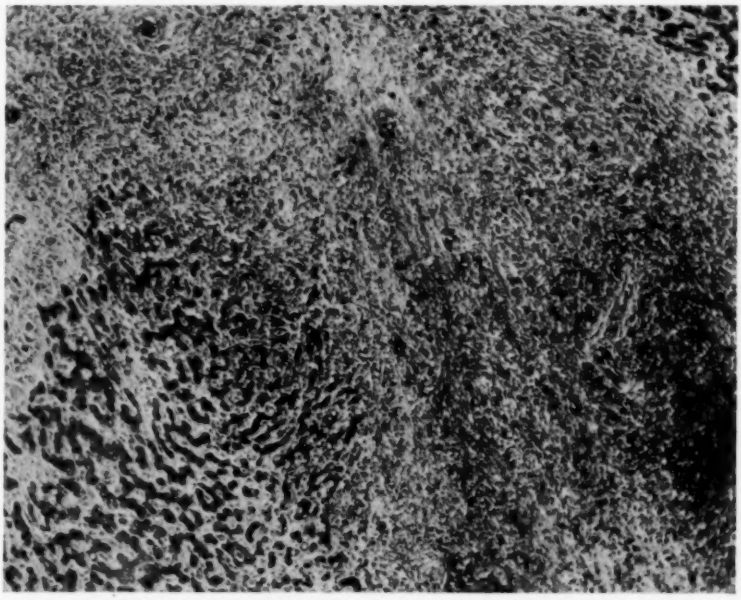

Fig. 5.—Photomicrograph, liver. The mixture of granuloma, liver atrophy, and necrosis is seen in the widened portal area. (Hematoxylin and eosin; ×110.)

throat and bone marrow and from post-mortem samples of liver, spleen, mesenteric nodes, and intestinal lymph nodes, a fungus which has the general characteristics of Histoplasma, and which produces an elongated tuberculo-spore which has the characteristics of *Histoplasma pyriforme*.

DR. FARBER.—This is the first case of generalized histoplasmosis in the history of our hospital. It is interesting that we should have to draw from so far afield for our first experience in this disease. Perhaps this is a spontaneous tribute to our salubrious New England climate.

Medical Progress

THE ABNORMAL HEMOGLOBINS: CLINICAL AND HEMATOLOGIC ASPECTS

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THE demonstration by Pauling and his associates[1] that the sickling phenomenon was dependent upon the presence of an abnormal hemoglobin led to an intensive study of human hemoglobin in normal and disease states. These authors found that normal and sickle hemoglobin differ in electrophoretic mobilities and that these were based on the number and kind of ionizable groups located in the globin component rather than in the heme. Rapidly accumulating data resulted in the identification of increasing numbers of abnormal hemoglobins and provided evidence that they were genetically controlled. This added information documented the concept that the clinical and pathologic features of many of the hereditary hemolytic disorders are basically conditioned by the abnormalities in the hemoglobin molecule.

The present paper summarizes the essential features of the principal clinical states and hematologic aspects of the abnormal hemoglobins from a pediatric background at which age group the majority of these syndromes are initially encountered. The description of specific hereditary hemoglobinopathies necessitates a preliminary consideration of methods by which the abnormal hemoglobins are identified and an analysis of their genetic transmission.

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METHODS FOR DETERMINING THE HEMOGLOBIN TYPES

Two simple procedures serve to identify the various types of hemoglobins: the detection of fetal hemoglobin by the method of alkali denaturation and the separation of the abnormal hemoglobins by the technique of paper electrophoresis.

ALKALI DENATURATION METHOD FOR FETAL HEMOGLOBIN (Hb. F)

The fetal hemoglobin content is determined as described by Singer and co-workers[2] in the "one-point" denaturation technique. In this technique, an approximate 10 per cent hemoglobin solution is denatured for exactly one minute by N/12 NaOH, the reaction being halted and the denatured hemoglobin precipitated by the addition of a 50 per cent saturated ammonium sulfate reagent. The hemoglobin concentration in the filtrate

(undenatured) is determined photoelectrically and the percentage of undenatured or alkali resistant hemoglobin (fetal hemoglobin) is calculated.

ELECTROPHORESIS

The migration of charged particles in an electrolyte solution which takes place when an electric current is passed through the solution is termed electrophoresis. In this process, particles bearing positive charges migrate to the cathode, while negatively charged particles move to the anode. This principle has provided a means by which plasma proteins and, more recently, hemoglobin solutions exposed to an electric field under selected conditions are separated in accordance with their isoelectric points and the individual mobilities of each constituent. The speed and direction of forward migration depend upon the type of solution used to conduct the electric current, its pH, the ionic strength, and the strength of the electric current.

The moving boundary method of Tiselius previously extensively employed has been recently simplified with the use of paper electrophoresis. With the latter a strip of filter paper properly prepared permits the differentiation of serum proteins and of hemoglobins according to their different velocities. In contrast to the use of an acid pH (cacodylate buffer of pH 6.5) for the method of moving boundary electrophoresis, the filter paper method of zone electrophoresis employs an alkaline buffer of pH 8.6 in which negatively charged protein particles move toward the positive electrode—the anode. With the contemporary interest in the relationship of abnormal hemoglobins to the hereditary hemolytic anemias, paper electrophoresis has provided a readily accessible tool in their identification. This method incorporates certain basic features which can be briefly outlined, but for detailed information reference should be made to recent papers and reviews.

In the paper method, the strip is maintained in the horizontal position or is raised in the middle by suspension on one or more supporting rods. In either case, the paper is saturated with buffer solution, the ends dipping into containers of the same solution. In the horizontal type of paper electrophoresis, a length of filter paper wet with buffer solution rests on a plate of glass or plastic material, with projecting points for support, the overlapping ends of the paper dipping vertically into troughs filled with the same solution. In adjacent compartments at each end are placed the respective electrodes. Before covering, minute quantities of the red cell hemolysate to be tested, prepared from the hemolysis of red cells in distilled water, are applied to the filter paper close to the cathodal end. In a solution of veronal buffer pH 8.6, ionic strength of approximately 0.06, and a specified voltage and current flow, the various hemoglobins migrate toward the anode according to their individual mobilities. After an initial period of two to three hours the hemoglobins have separated sufficiently to be recognized, the length of the complete run (usually four to six hours) depending upon the particular requirements of the laboratory. At the end of the separation the

strips are removed and dried and amounts of each hemoglobin may be roughly estimated or accurately measured.

DESIGNATION OF HEMOGLOBIN TYPES

Recommended nomenclature designates the capital letters A for normal adult, F for fetal, and S for sickle-cell hemoglobin, and consecutive letters of the alphabet for either abnormal types in order of their identification. Case reports have established the importance of types C, D, and E,

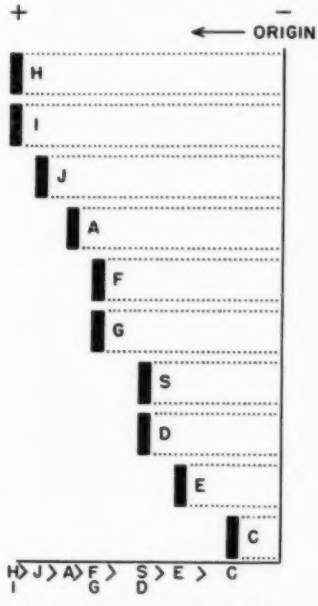

Fig. 1.—Schematic representation of relative mobility of abnormal hemoglobins.

which occur in association with well-defined hematologic entities. The racial incidence of hemoglobins is exemplified by the predominance of the abnormal hemoglobins—S and C in Negroes and E in natives of Thailand.

ELECTROPHORETIC MOBILITY OF THE INDIVIDUAL HEMOGLOBINS

According to the specific conditions prescribed for paper electrophoresis of the common hemoglobin types, hemoglobins H and I move farthest toward the anode and C is the slowest, remaining nearest the starting point. Intermediate between A and C, in descending order of slower mobility, are the hemoglobins F, G, S, D, and E. F is imperfectly separated from A unless appearing in great excess. S and D have identical mobilities. In its homozygous form G migrates at a single focus between S and F and is differentiated from the latter by its lack of resistance to alkali denaturation.[3] The mobility of H and I is greater than A, appearing closest to the anodal end of the filter paper. The recently described hemoglobin J[4] possesses an electrophoretic mobility between hemoglobins I and A.

The relative mobility rates are summarized and schematically represented in Figs. 1 and 2.

FETAL HEMOGLOBIN

Important biochemical differences exist between adult hemoglobin and the form elaborated by the human fetus during prenatal life. While the heme component of the two hemoglobin molecules is similar, the differences relate to the structure and properties of globin and possibly of the hemoglobin linkages. The property by which fetal hemoglobin is best known and most readily identified is its increased resistance to denaturation by alkaline solutions.

Fetal hemoglobin, which comprises 44 to 89 per cent of the hemoglobin

in the newborn infant,[5] decreases rapidly during the first year of life and is rarely demonstrable after the age of 30 months.[6] Following this period and in the child and adult, 2 per cent represents the upper limit of normal. In certain of the chronic hereditary hemolytic disorders fetal hemoglobin reappears in substantial amounts. Large quantities of fetal hemoglobin are synthesized in patients with sickle-cell anemia (5 to 15 per cent) verity of the disease. Since multiple transfusions tend to depress its production, true estimates of its concentration can only be made during treatment-free intervals or prior to the initiation of blood administration.[7]

The presence of high concentrations of fetal hemoglobin in early infancy apparently precludes the presence of either sicklemia[8] and of hemoglobin C.[9] The appearance of each of these hemoglobins was found to be delayed

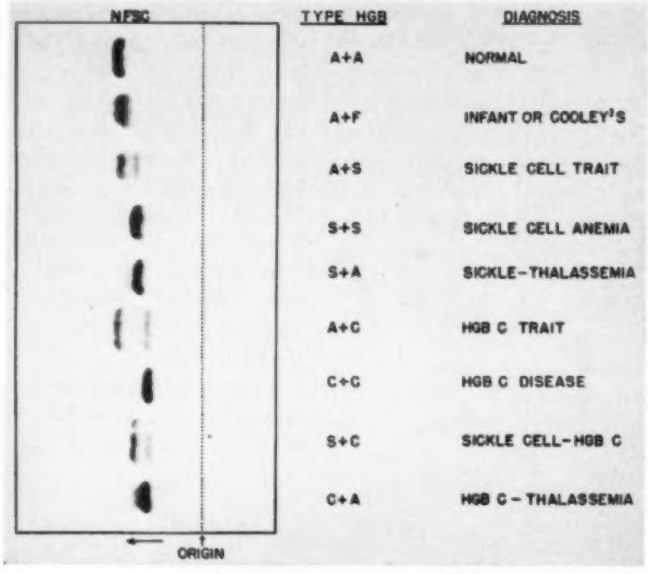

Fig. 2.—Electrophoretic patterns of the common hereditary hemoglobinopathies.

and severe Mediterranean anemia and to a lesser extent in spheroeytie anemia (usually less than 10 per cent).[2] The highest concentrations of alkali-resistant hemoglobin are found in severe Mediterranean anemia where it may represent almost the entire hemoglobin content (12 to 100 per cent). The reason for these excessive amounts of embryonic hemoglobin is unknown and cannot be correlated with the severity of the disease. until the infant was 6 and 4 months of age, respectively, when the fetal hemoglobin normally drops to lower levels.

Fetal hemoglobin may be elevated in pure red-cell anemia (chronic congenital aregenerative anemia), acute and chronic leukemia, and in metastatic carcinoma involving the bone marrow. Normal values are present in iron-deficiency anemia and in acquired hemolytic anemia.[2]

PRIMITIVE HEMOGLOBIN (P)

Fetal hemoglobin is to be differentiated from the primitive type (P) which is found in early fetal life.[10] This hemoglobin with an electrophoretic mobility on filter paper slower than those of the adult and fetal hemoglobins prevails during the first half of embryonic life and is later replaced by fetal hemoglobin. The primitive hemoglobin is associated with severe hypoproteinemia and agammaglobulinemia but its biologic significance awaits further study.[11]

COMPENSATED HEMOLYTIC DISEASE AND ANEMIA

The capacity of the bone marrow to respond to varying degrees of blood destruction constitutes an essential part in evaluating the hematologic status of the patient with a hereditary hemoglobinopathy. Crosby and Akeroyd[12] have pointed out that abnormal degrees of hemolysis need not result in anemia if the bone marrow is capable of regenerating adequate amounts of hemoglobin and red blood cells. Its capacity has been estimated at six to eight times the normal, which permits an average red-cell survival of only fifteen to twenty days instead of the normal of 120 days without anemia. Anemia results when the mean red-cell life falls below these limits, when the bone marrow is unable to respond with maximal capacity, or when both factors are involved. In the event of anemia, equilibrium is re-established at lower levels.

While homozygous sickle-cell disease and thalassemia major or severe Cooley's anemia are severe hemolytic diseases, it has been demonstrated that the rates of hemoglobin production vary widely in the two diseases.[12, 13] The hemoglobin output of three times the normal in Cooley's anemia as compared with five to six times the normal in sickle-cell anemia explains the greater need for transfusions in the former disease. The elevated reticuloeyte count affords a useful index of increased bone marrow activity in the absence of overt anemia. In crises of sickle-cell anemia, for instance, the lowered precritical hemoglobin levels may remain unchanged, but the reticuloeytes may be elevated to indicate accelerated bone marrow activity to compensate for the increase in hemolysis. Added features of excessive activity often without anemia include the presence of nucleated red cells in the peripheral blood, bilirubinemia, and increased urobilogen excretion in the stools.

HEREDITARY ASPECTS

One of the first steps in the diagnosis and in appraisal of the degree of involvement in a suspected case in this group is the search for specific hemoglobins in the affected individual and in other members of the family.

The principles relating to the familial distribution of the genes for the normal and abnormal hemoglobins conform to the basic principles of heredity. In the somatic cells of the body the genes are paired, one member of each pair being derived from a single parent. The members of a pair of genes are termed alleles and occupy similar positions or loci on a pair of homologous chromosomes. The homozygous individual receives an identical gene for the particular hemoglobin from both parents, while

the heterozygote receives different, contrasting, or alternate members of genes or alleles. In the homozygous state both genes of the pair are either normal or abnormal and in the heterozygous individual one of the genes is normal, the other abnormal. In the case of abnormal hemoglobins the double heterozygous state is one in which the genes determining the two hemoglobins differ from each other. In exceptional cases of thalassemia-sickle-cell disease and of hemoglobin C-thalassemia, other patterns of genetic transmission than multiple alleles are to be considered. These rare instances involve such chromosomal relationships as linkage in which genes are located in two different chromosomes, permitting independent transmission.

Comprehensive family pedigrees will frequently elucidate not only the hematologic picture in the patient but of other closely related persons who are asymptomatic or who have suffered from a mild but unexplained anemia. Numerous family studies have demonstrated that with the exception of fetal hemoglobin the genes responsible for the abnormal hemoglobins are alleles of those for normal hemoglobin.

The gene for any one of the abnormal hemoglobins may thus replace one or both genes for normal hemoglobin. When only one normal gene is replaced, the individual is regarded as a carrier possessing a heterozygous hemoglobin trait. Homozygous or pure hemoglobin disease results when both genes for hemoglobin A are replaced by those of the same abnormal hemoglobin. With few exceptions, family studies have demonstrated that hemoglobins S, C, D, and E represent alleles of normal hemoglobin A.

RELATION OF GENETIC COMPOSITION TO CLINICAL-HEMATOLOGIC VARIATIONS

Expressivity of a gene refers to the variability of its expression in different individuals and explains certain of the quantitative aspects observed in the inheritance of the abnormal hemoglobins. It has been postulated that the amount of a particular hemoglobin in a blood sample is influenced by interaction with the gene controlling another type of hemoglobin with which it is combined. Thus the gene for Cooley's anemia permits the appearance of amounts of sickle-cell hemoglobin when the two diseases are combined as high as 80 per cent in the offspring despite the presence in the parent of less than 50 per cent of this component. This augmenting influence seen also in the interaction of the gene for Cooley's anemia with the genes for either hemoglobin C or E will be elaborated later in the text.

The intensity of each syndrome varies from the asymptomatic or mild case, in which a single abnormal hemoglobin is present in the heterozygous state in combination with one of the two allelic genes for normal hemoglobin, to the severely anemic individual, in whom two identical abnormal hemoglobins appear in the homozygous state.

Intermediate grades of hemolytic disease are associated with the presence of two different abnormal hemoglobins—the mixed or double heterozygous state. Their simultaneous presence results in a hemolytic anemia of variable intensity, together with moderate splenomegaly and pe-

ripheral blood changes of both diseases. While a single dose of a gene for abnormal hemoglobin produces the trait or mild disease and a double dose the severe disease, the degree of clinical and hematologic changes cannot be exactly correlated with one particular mixture of abnormal hemoglobins. Thus Cooley's anemia and sickle-cell anemia representing the homozygous state in each disorder are more severe clinically and hematologically than either homozygous C or E disease.

Prior to the discovery of abnormal hemoglobins it had been established that the gene responsible for Cooley's anemia or thalassemia occurs once in the heterozygote or mild disease and twice in the homozygous or severe disease. A similar pattern of inheritance was postulated for sickle-cell disease,[14] namely, that the gene responsible for sickling is present in the heterozygous sickle-cell anemia. Exceptions to this genetic pattern, namely, the failure to find similar recognizable blood changes in each parent of an affected child with either Cooley's anemia or sickle anemia, can now be explained by the presence in the dissimilar parent of another unrelated abnormal hemoglobin.

TARGET CELLS

Target cells are particularly prominent in the blood smear of patients with abnormal hemoglobins and often provide a clue to diagnosis. This distinctive feature is particularly suspicious in the Negro patient of the presence of abnormal hemoglobins. Present in both mild and severe Mediterranean anemia (usually up to 10 per cent) they are further increased in sickle-cell anemia and appear in even larger numbers than each separately when they are combined (microdrepanocytic or thalassemia-sickle-cell disease). In sickle-cell-hemoglobin C disease they are present to the extent of 40 to 90 per cent of all red cells. It has been suggested that large numbers of target cells in the blood smear indicate the presence of C hemoglobin. Target cells are also increased in hemoglobin E disease, perhaps less than with C hemoglobin. Few or none of these cells are noted in reported cases of sickle-cell-hemoglobin D disease,[15] or with G, H, I, and J hemoglobins.

SYNDROMES ASSOCIATED WITH THE ABNORMAL HEMOGLOBINS

Investigation of the physiochemical properties of the hemoglobin molecule has been particularly revealing in explaining the variability in the clinical, hematologic, and genetic aspects of sickle-cell disease and Cooley's anemia. These studies have demonstrated that each of these diseases exist not alone as in the classical homozygous forms with well-known manifestations but as their variants. The latter though less severe nevertheless simulate them clinically and hematologically. The differences can now be explained on the basis of the simultaneous presence of another hemoglobin. Thus the majority of abnormal syndromes to be described are initially diagnosed either as Cooley's anemia or sickle disease.

The designation of thalassemia for Mediterranean or Cooley's anemia has shown increasing usage with the recognition of the combined hemoglobins. Although the terms thalassemia major and minor may meet

with some reservations, nevertheless the use of the term thalassemia lends itself to the hyphenated descriptions of the various abnormal hemoglobins with which it may be combined.

Brief comment will be made with regard to the more important syndromes involving abnormal hemoglobins. For the interested reader, further details will be found in individual papers and in the excellent and comprehensive reviews now available.[16-21]

The multiplicity of combinations of the abnormal hemoglobins in the heterozygous, double heterozygous, and homozygous states precludes a discussion confined exclusively to a single abnormal hemoglobin so that overlapping comments are inevitable.

SYNDROMES INVOLVING SICKLE HEMOGLOBIN (HEMOGLOBIN S)

Current thought attributes the sickle-cell abnormality to a mutant gene which is responsible for the synthesis of a type of hemoglobin different from normal hemoglobin. The peculiar shape of the erythrocytes in sickle-cell disease is related to the altered alignment of the abnormal hemoglobin molecules in the anoxic state. The distortion on sickling has been attributed to the greatly decreased solubility of reduced sickle-cell hemoglobin as compared with reduced normal hemoglobin. This results in intracellular crystallization[22] or increased viscosity with tactoid formation producing the well-known sickled configuration.[23] The shape is reversible. The filamentous form of the sickled cell in an environment of lowered oxygen tension resumes the biconcave disk when normal oxygen tension is restored. A minimal value of 7 per cent intraerythrocytic concentration of S pigment is required to elicit the sickling phenomenon.[24] In this case the carrier may therefore show a negative sickling test with sickle hemoglobin demonstrable by electrophoresis.

The sickling in the homozygous sickle-cell anemia (S-S) and in other forms of sickle-cell disease (thalassemia-sickle-cell and sickle-cell-hemoglobin C disease) is rapid and assumes chiefly a filamentous form. In sickle-cell trait, sickling is slower and a holly-leaf rather than filamentous form predominates.

The observed shortened survival of red cells containing abnormal hemoglobin in this and other hemoglobinopathies results from structural changes which they induce.

It has recently been shown that the impairment of urine concentration (hyposthenuria) commonly found in sickle-cell anemia results from the presence of intravascular sickle-cell hemoglobin. The ability to concentrate could be restored to normal following multiple transfusions of normal red cells.[25]

Sickle-Cell Trait.—The trait representing the heterozygous state (A and S hemoglobins) occurs in approximately 9 per cent of American Negroes. A small number, about one in forty of those with sickling, show sickle-cell anemia. The frequency of the trait in some African tribes has been given as high as 45 per cent. The trait or sicklemia can be demonstrated in vitro by the ability of the erythrocytes to sickle when oxygen tension is lowered. This is accomplished by a variety of techniques such as sealing a drop of fresh blood under a cover slip with petrolatum or

more rapidly by mixing the blood with a reducing agent such as 2 per cent sodium bisulfite. The amount of sickle-cell hemoglobin in the trait as determined by electrophoresis varies from 24 to 45 per cent of the total hemoglobin.[26] Target cells are present in small numbers. Individuals with the trait are not anemic, show no physical abnormalities, and are usually asymptomatic. Evidences of vascular occlusion by sickled cells have been reported in a few patients with the sickle trait resulting from moderate or high altitudes.[27-30]

Allison[31] postulated that the loss of the sickle-cell gene by early death of patients with homozygous sickle anemia was counterbalanced by the resistance of individuals with sickle-cell trait to become infected with malaria. This concept of a selective or reproductive advantage for the heterozygote over the normal individual (balanced polymorphism) he also extended to thalassemia, since many of the cases of this disease come from districts severely affected with malaria.

Sickle-Cell (Drepanocytic) Anemia.—Sickle-cell anemia is a chronic hemolytic disease usually initially diagnosed in childhood and occurring in homozygous individuals who have inherited the sickle-cell gene from both parents. The bulk of hemoglobin (60 to 98 per cent) is of the S variety, the remainder consisting of fetal (F) hemoglobin (usually 2 to 24 per cent). Hemoglobin A is absent unless the patient has been recently transfused. The anemia is chronic, normochromic, and normocytic, target cells are increased, osmotic fragility decreased, and the red cells have a shortened survival time. Patients with sickle-cell anemia maintain a relatively stable hemoglobin level with equilibrium established at from 6 to 8 grams, so that multiple transfusions are unnecessary. Increased mechanical fragility of sickled cells contributes to the anemia.[32] Hyperbilirubinemia and a reticulocytosis more marked (5 to 20 per cent) than in homozygous thalassemia disease is indicative of a hyperactive bone marrow. Reticulocytes are decreased in the infrequent aplastic crises. The stained smear shows varying numbers of sickled cells sometimes surprisingly few but with 100 per cent sickling, using one of the standard deoxygenation techniques. Sickle cells (drepanocytes) may be crescent or holly-leaf in appearance in sickle-cell variants, but in the homozygous disease, characteristically elongated, filamentous, and pointed at each end, curved in the middle, and containing a full complement of hemoglobin.

Splenomegaly, which is occasionally present in children, is usually absent in the older individual. The incidence has been given as 33 per cent in the first decade of life and 10 per cent thereafter.[33] Splenomegaly, while not uncommon in sickle-cell anemia, appears to be much more frequent in sickle-cell-hemoglobin C disease and in sickle-cell-thalassemia disease. Atrophy of the spleen occurs with advancing age and is due to infarction from sickling. An enlarged spleen is often associated with shortened survival of transfused normal blood.

Crises are characterized by fever, pain in the joints, bones, and abdomen, and frequently by no exacerbation of the anemia. In children a crisis has been observed to be associated with a sharp shrinkage of the

plasma volume so that the peripheral hemoglobin concentration may actually be elevated. Furthermore, the anemic patient with this disease has a blood volume far in excess of the normal in periods of freedom from disability.[34] As would be expected, in restoring expanded plasma levels, during treatment with whole blood, plasma, or dextran, the hemoglobin level may actually drop.

Sickling of the red cells occurs in areas of lowered oxygen tension such as prevails in the terminal capillaries. Erythrostasis and increasing viscosity with occlusion of vessels by sickled cells are responsible for the diverse symptom complexes suggesting rheumatic fever, osteomyelitis, appendicitis and other surgical diseases of the abdomen. In contrast to the hemolytic crisis, in which a sudden destruction of blood is accompanied by a hyperfunctioning bone marrow, is the occurrence of an aplastic crisis. In the latter, anemia develops rapidly due to a cessation of red cell production and the continued destruction of sickled cells in the circulation.

Transfusions need rarely be given except during crises. Splenectomy is indicated for massive enlargement of the spleen and especially for cases in which an extracorpuscular hemolytic factor as indicated by increased transfusion requirements for donor blood has been demonstrated.

THALASSEMIA (MEDITERRANEAN OR COOLEY'S ANEMIA)

This entity originally described by Cooley and his associates combines the features of a refractory hemolytic anemia with characteristic roentgenographic, clinical, and blood changes. The anemia presents a wide spectrum of severity—the trait, moderate and severe type termed thalassemia minor and major at each extreme. Additional gradations are sometimes designated, such as thalassemia intermedia, for a less marked anemia than the severest type and thalassemia minima for the mildest.

RACIAL DISTRIBUTION

While the majority of patients in this category have a Mediterranean ancestry—Italy, Syria, and Greece—scattered reports have shown their wide geographical and racial distribution, including the Chinese, Asiatic Indians, Egyptians, natives of Thailand, and among Negroes.

GENETIC TRANSMISSION

The individual with the trait or mild disease, who functions as a carrier, is regarded as heterozygous for a gene which, when homozygous, produces the severe disease. The gene for thalassemia has a varying expressivity for the grade of anemia and it is sometimes difficult to separate the moderate from the severe type hematologically since the latter with a bilateral inheritance occasionally overlaps the former as a heterozygote. In both instances a minimum of transfusions may be needed to support hemoglobin levels. The presence of the trait in only one parent of a child with the severe disease should prompt a search for sickle cell, hemoglobin C or E disease in the second parent, and of the combined disease with the respective hemoglobin in the patient.

FETAL HEMOGLOBIN IN THALASSEMIA

The fundamental defect in this disease consists of an inability to synthesize adult hemoglobin in normal amounts. This may involve both a defect in structure and an inability to

incorporate iron in the molecule. The decreased survival of the red cells of patients with the severe disease reflects deficiencies in structure conditioned by defective hemoglobin. In the severe disease, hemoglobin analysis reveals an extraordinary percentage of the fetal type with values ranging to 40 and 100 per cent. In parents and asymptomatic siblings with the trait of the disease, fetal hemoglobin falls within the usual range. With overnight electrophoresis, fetal hemoglobin can be demonstrated when present in substantial amounts as a slower component than normal hemoglobin and almost continuous with it.

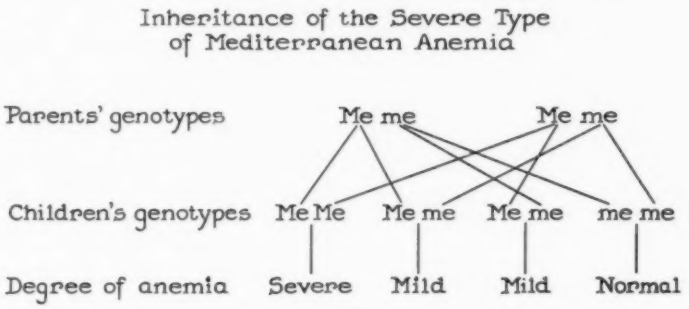

Fig. 3.

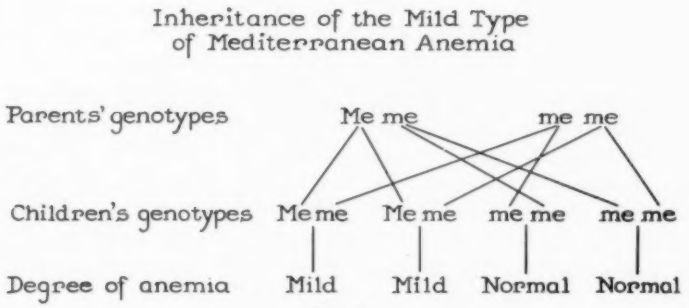

Fig. 4.

Figs. 3 and 4.—Example of genetic transmission when both parents are heterozygous for the same gene (Fig. 3) and when one parent is heterozygous and the other normal (Fig. 4). The gene involved in each instance is for Mediterranean anemia (thalassemia). The designation of ME-me, the heterozygote, is a simplification of current terminology for this disease. According to a proposed nomenclature[10] the genotype of the heterozygote is $Hb^A/Hb^A:Th^N/Th^T$. Th^N is the normal allel of the thalassemia gene Th^T, while Hb^A is the gene for normal hemoglobin. In this diagram "Me" corresponds to Th^T and "me" to Th^N.

TABLE I. GENETIC CONSTITUTION OF CLINICAL TYPES OF MEDITERRANEAN (COOLEY'S) ANEMIA

DEGREE OF ANEMIA	GENOTYPES
Severe	Me Me
Trait or mild anemia	Me me
Normal	me me

Me is gene for Mediterranean anemia.
me is contrasting normal allele.

EFFECT OF THE GENE FOR THALASSEMIA UPON OTHER HEMOGLOBINS

Except for the elevation of fetal hemoglobin, which occurs in smaller amounts in many conditions, no specific abnormal hemoglobin has been described in this disease. No rela-

tionship has as yet been demonstrated between the amount of fetal hemoglobin and the severity of the disease. The gene for thalassemia either interferes with the normal suppression of fetal hemoglobin or the latter is formed in place of the more difficult synthesis of the adult type of pigment. The excessive amounts of hemoglobin S, C, and E present when they occur in combination with thalassemia may reflect a compensatory replacement of normal hemoglobin whose synthesis is retarded by the gene for thalassemia. These increased concentrations may also reflect the potentiating effect of the gene for thalassemia on the formation of abnormal hemoglobin as already postulated.

CLINICAL FEATURES

While the mild form is asymptomatic and can only be detected by blood examination, the severely anemic patient presents a pathognomonic facial appearance and other physical abnormalities. Splenohepatomegaly is marked in the severe disease. Cholelithiasis occurs infrequently.[35] In persons with the moderate disease, the spleen may be slightly enlarged and in the mild form not at all.

HEMATOLOGIC FINDINGS

On laboratory examination increased resistance of red cells to hemolysis in hypotonic solutions of sodium chloride is found in all forms of Mediterranean anemia, mild and severe alike. In the trait and mild type, hypochromic macrocytes, microcytes, basophilic stippling, polycythemia, and target and oval cells are seen. Morphologic changes far in excess of the degree of anemia characterize the mild form. An increased percentage of eosinophilic leukocytes is frequently found in the blood smears of patients with the trait. The degree of stippling may simulate lead poisoning. Very large, thin, hypochromic macrocytes (leptocytes), nucleated red blood cells, marked anisocytosis and poikilocytosis, target and oval cells are prominent in the blood smear of the severe disease. Although hypochromic macrocytes characterize both the mild and severe disease, red cell constants indicate a microcytic hypochromic anemia. The sometimes increased hemoglobin and polycythemic red cell values encountered in the siblings and parents with the mild form of Mediterranean anemia reflect a state of compensated hemolytic disease by an overactive marrow. The bone marrow in severe cases shows a predominance of nucleated red cells which is less marked in the mild or moderate form. The increase of nucleated red cells in the peripheral blood following splenectomy which is so marked in this disease probably reflects the removal of an inhibiting influence from the bone marrow where these cells predominate.

Red Cell Survival.—The intracorpuscular defect of the red cells is clearly shown by transfusion experiments. The red cells of the patient with the severe disease are rapidly eliminated on transfusion into a normal donor and within its own circulation. A shortened survival of transfused normal donor erythrocytes is observed in patients with intact spleens. With few exceptions, the age of the patient influences red cell survival to the extent that transfused blood is more rapidly eliminated from

the circulation with advancing age,[36] with a more normal survival in the younger patients.

PROGNOSIS AND TREATMENT

Multiple transfusions at carefully spaced intervals, splenectomy in selected cases, and the liberal use of antibiotics permit a better prognosis in the severe cases than had heretofore been considered. Since the application of these combined measures is relatively recent, their effect on ultimate longevity has still to be determined. Nevertheless, it is not unusual for severely affected patients to survive into adult life. Hemosiderosis and the possible progression into hemochromatosis may lead to serious complications by interfering with tissue function.

HOMOZYGOUS HEMOGLOBIN C DISEASE

This is a rare condition occurring principally in Negroes, occasionally in Caucasians.

Essential Features.—Anemia is absent or mildly hemolytic, reticulocytes are normal or slightly increased, slight elevation of bilirubin may be present—features indicative of a compensated hemolytic process. The red cells are normocytic or slightly microcytic and normochromic, normoblasts occasionally appear and tetragonal crystals of hemoglobin have been observed in one case in 2 per cent of the erythrocytes.[37] Red cells show a decreased osmotic fragility. Moderate erythrocytic hyperplasia is present in the bone marrow. The striking feature of the blood film is the large number of target cells estimated at 40 to 90 per cent of all erythrocytes. Paper electrophoresis reveals 100 per cent hemoglobin C, which has the slowest mobility rate of all hemoglobins as tested by this technique. With rare exceptions, fetal hemoglobin is not elevated above normal levels. As with other hereditary hemolytic syndromes, the red cells from patients injected into a normal recipient shows a shortened survival. The exponential type of survival time curve indicates the random destruction of red cells regardless of their age.[9] Splenomegaly is either moderate or very marked. Abdominal pain, arthralgia, jaundice, and cholelithiasis are uncommon. The prognosis is good and transfusions are rarely necessary. Splenectomy is occasionally carried out for relief of symptoms relating to pain over the splenic area.[38]

HEMOGLOBIN C TRAIT

The combination of A and C hemoglobins is found in the asymptomatic carrier who is identified by electrophoresis and the presence of numerous target cells in the blood smear. In the individual with the trait the C pigment varies from 28 to 44 per cent, sickling is absent, fetal hemoglobin is normal, and a mild hypochromia may be present. The hemoglobin C trait is detected in about 2 per cent of the American Negro population.

HEREDITARY ELLIPTOCYTOSIS AND HEMOGLOBIN C TRAIT

Two children in a Negro family were found to have both elliptocytosis and hemoglobin C. Each of these factors was traced to the respective parents. In one child some of the target cells associated with the hemoglobin C trait were elliptical, indicating the combined genetic effects in the same cell. Anemia in one child

was corrected by iron and the red cell survival was normal. The combination of elliptocytosis and hemoglobin C trait does not show a summation effect.[39]

HEMOGLOBIN D

This rare hemoglobin possesses an electrophoretic mobility identical with sickle hemoglobin.[63] It is distinguished by its much higher solubility in reduced form than the latter in a comparable state. Homozygous hemoglobin D has not been described.

The individual with the trait (hemoglobin A and D) is asymptomatic and reveals no quantitative blood changes and no sickling. He can only be identified by the presence of D hemoglobin by electrophoresis.

HEMOGLOBIN E DISEASE

Hemoglobin E disease was discovered in investigating a group of severely anemic patients from Thailand whose clinical and hematologic characteristics closely resembled cases of severe thalassemia. In some of these individuals a mild course and survival into adult life suggested deviation from the uniformly severe case of thalassemia. A significant feature was the presence of the trait of thalassemia in only one parent instead of in both which was to be expected in the usual case of the severe disease in a child. Investigation revealed that these patients possessed an additional hemoglobin designated as compound E, which was also present in the second parent. With paper electrophoresis it was possible to demonstrate that hemoglobin E had a mobility intermediate between hemoglobin C and S. Further studies[40, 41] revealed the several categories of pure or homozygous hemoglobin E disease, hemoglobin E trait (hemoglobin A plus hemoglobin E) and thalassemia-hemoglobin E disease. A survey in connection with these studies revealed that hemoglobin E was found in 13 per cent of individuals of Thai extraction but was not detected in any of the racially unmixed Chinese in that area.

HOMOZYGOUS E DISEASE

The clinical features include easy fatigability, mild arthralgia, and occasional icterus. In the small group of cases in this category the spleen was slightly enlarged in only one patient and the liver in another. The hemoglobin is moderately lowered, the erythrocyte levels are normal, reticulocytes not increased, target cells are numerous (25 to 60 per cent). Red cell constants indicate a microcytic hypochromic anemia. The red cells show an increased resistance to hemolysis in hypotonic saline solutions. The bone marrow shows a mild erythrocytic hyperplasia. Paper electrophoresis reveals 94 to 98 per cent hemoglobin E and up to 6 per cent fetal hemoglobin.

HEMOGLOBIN E TRAIT

Individuals with the trait are asymptomatic. Blood values are normal and target cells are not observed. Paper electrophoresis reveals two components: normal hemoglobin A and hemoglobin E. Normal amounts of fetal hemoglobin are demonstrated by alkali denaturation.

HEMOGLOBIN G

This pigment moves more slowly than hemoglobin A and faster than hemoglobin S, corresponding electro-

phoretically to the area in which fetal hemoglobin is found.[42] Its mobility coincides with fetal hemoglobin or migrates somewhat more slowly. Hemoglobin G is not alkali-resistant and can be differentiated from fetal hemoglobin in this manner.[43]

HEMOGLOBIN G TRAIT

In a family from the African Gold Coast, in which the parents were homozygous for hemoglobins A and G, respectively, nine siblings as expected were heterozygous (A-G).[44] These individuals with the trait presented no clinical or hematologic abnormalities.

HOMOZYGOUS G DISEASE

The father of the above family (GG) was asymptomatic, not anemic (hemoglobin 13.9 grams) and the blood smear was free of abnormalities. Fetal hemoglobin was not present, reticulocytes were 2 per cent, and the serum bilirubin was normal.[44]

HEMOGLOBIN G-SICKLE-CELL DISEASE

With heterozygous hemoglobin G-sickle-cell disease, a moderately severe hemolytic anemia occurs with splenomegaly, sickling, increased osmotic resistance to hypotonic saline and a blood picture resembling sickle-cell-thalassemia disease.[43]

HEMOGLOBIN G-THALASSEMIA

The Italian patient with this condition possessed a blood picture and clinical findings somewhat more severe than thalassemia minor. The hemoglobin was 10 grams and the smear revealed hypochromic red cells, target cells, and basophilic stippling. Other features included no elevation in fetal hemoglobin, slight reticulocytosis, a palpable spleen, and moderately hyperplastic bone marrow. The red cell survival was about two-thirds of the normal.[45]

HEMOGLOBIN H

Three members of a Chinese family were found to have a hypochromic, microcytic anemia with blood smears resembling thalassemia. The electrophoretic pattern revealed an abnormal hemoglobin migrating more rapidly than normal (A) hemoglobin. Other features included refractoriness to iron therapy, reticulocytosis, poikilocytosis, intraerythrocytic inclusion bodies, decreased osmotic fragility, a shortened red cell survival, and splenomegaly.[46] The abnormal hemoglobin accounted for 35 to 40 per cent of the total, fetal hemoglobin was slightly increased, and the remainder was normal hemoglobin.

A similar blood picture interpreted as hemoglobin H-thalassemia disease has been described in two unrelated Filipino middle-aged males. Hemoglobin analysis in these cases revealed the major component as hemoglobin H. Fetal hemoglobin was normal.[47]

HEMOGLOBIN I

A hemoglobin with a mobility more rapid than normal hemoglobin A was detected in several members of a Negro family. The affected individuals were asymptomatic and showed no hematologic abnormalities.[48] This hemoglobin was present in equal amounts with hemoglobin A. Differences in mobility between hemoglobins H and I which were not apparent at pH 8.6 were clearly distinguishable at pH of 6.5.

HEMOGLOBIN J

This hemoglobin, observed in a Negro family, was shown to have a more rapid electrophoretic mobility at a pH 8.6 than normal adult hemoglobin but slower than the next component I. It was found in combination with normal hemoglobin. Sickling was absent and no hematologic or physical abnormalities were found.[4]

Two hemoglobin types have been observed in Liberian natives, one with a mobility corresponding to J, the other between J and A. No cytologic abnormalities were found in either case.[64]

SICKLE-CELL VARIANTS

Sickle-Cell-Thalassemia Disease (Microdrepanocytic Anemia).—This combination accounts for most of the cases of sickle-cell disease in white persons, usually of Greek or Italian origin, although it has been reported in American Negroes.[49] Such a patient usually inherits the gene for thalassemia from one parent and for sickle-cell hemoglobin from the other. Rare exceptions[50] include instances in which one parent with sickle-cell-thalassemia disease, the other being normal, transmits both of the abnormal factors to the offspring. In another instance a normal offspring resulted from one parent with the combined disease and the other normal. Electrophoretic studies reveal the presence of sickle, normal, and occasionally fetal hemoglobin. The percentage of sickle hemoglobin ranges between 65 and 80 per cent (in one case 90 per cent), which is less than the 75 to more than 85 per cent present in homozygous sickle-cell anemia.[51] Hemoglobin analyses by electrophoresis and alkali denaturation have demonstrated that thalassemia-sickle-cell disease consists of hemoglobins S, A, and F or hemoglobins S and A. Homozygous sickle-cell anemia, on the other hand, consists exclusively of sickle and fetal hemoglobins, the latter in amounts of 2 to 24 per cent.[52] The higher percentage of sickle-cell hemoglobin in the offspring than in the parent with the trait (25 to 45 per cent hemoglobin S) reflects the potentiating effect of the associated thalassemia gene. The disproportionate amount of hemoglobin S despite its presence in only one parent may also stem from the depression of normal hemoglobin synthesis by the thalassemia gene with corresponding increase of the abnormal hemoglobin. The clinical manifestations of the combined disease represent predominately a sickle type of hemolytic anemia although of lesser severity than the homozygous sickle-cell disease.

Essential Features: The blood smear shows thin hypochromic macrocytes, poikilocytosis, marked anisocytosis, oval cells, basophilic stippling, and, less frequently, normoblasts. Target cells are increased exceeding those in sickle-cell anemia. Sickle cells are few in number in the fixed smear but increased at times to 100 per cent in sickle-cell preparations. Osmotic fragility is decreased. Clinically and hematologically the disease presents itself as a moderate form of Mediterranean anemia, rarely of sickle-cell anemia. Anemia is moderate, hemoglobin 6 to 9 grams per 100 c.c., usually about 8 grams, and red cells number approximately 3 million. Red cell constants indicate a microcytic hypochromic anemia as in thalassemia. The other sickle-cell variants show normo-

chromic, normocytic red cell constants as in homozygous (S-S) sickle-cell anemia.

Clinical Findings: The clinical manifestations are less severe than either sickle-cell anemia or thalassemia major. Crises are rare, but abdominal, bone, and joint pain and at times unexplained fever occur. Severe cases occur occasionally as in sickle-cell anemia. Jaundice is mild, splenomegaly, mild to moderate. Aseptic necrosis of the head of the femur has also been reported.[53] Splenomegaly is much more common than in sickle-cell anemia but not as marked as in severe Cooley's anemia. Hepatomegaly may be of significant degree. Patients with this disease present themselves because of anemia and splenomegaly later in childhood than those with thalassemia major in whom these features are already advanced in the first year of life. Treatment depends on severity. In severe cases multiple transfusions are needed and, rarely, splenectomy if blood requirements are high. Mild cases require no treatment. Prognosis is better than in homozygous sickle-cell anemia.

Sickle-Cell-Hemoglobin C Disease.—The simultaneous presence of the sickle-cell gene and the gene for hemoglobin C results in a type of sickle-cell disease second in frequency only to classical sickle-cell anemia among American Negroes.[54] The evidence derived from genetic studies strongly points to the association of these genes as alleles or close linkage upon the same chromosomes.[55]

The clinical manifestations are usually of lesser severity than in homozygous sickle-cell anemia, but are extremely variable, ranging from an asymptomatic state to severe disability. In the category of hemoglobin S-C disease probably belong some of those patients heretofore regarded as milder cases of sickle-cell anemia. Crises are of lesser severity and infrequent, hepatomegaly is usually present, and splenomegaly is moderate or marked. Fatigue, dyspnea, jaundice, migratory arthralgia, recurrent abdominal pain may be present. Pregnancy seems to aggravate the clinical and hematologic signs and carries a greater risk than classical sickle-cell anemia. Aseptic necrosis of the humoral or femoral heads, splenomegaly which persists and may progress into adult life in contrast to the shrinkage of the spleen in sickle-cell anemia, hematuria, splenic infarction during aerial flights have been described in hemoglobin S-C disease.[56]

The anemia is usually of a mild, normochromic type, and the red cells vary slightly in size, being either normal or decreased in volume. The hemoglobin rarely falls below 8 grams, usually ranging from 9 to 10 grams, and red cells between 3.5 and 4.5 million. Antisocytosis and poikilocytosis are occasionally noted in severe cases. Crises are associated with normoblastosis, reticulocytosis, and increased numbers of white cells in the peripheral blood. Reticulocytes generally are normal or slightly elevated, serum bilirubin is normal, and osmotic fragility decreased. Erythroid hyperplasia which characterizes the bone marrow is not as marked as in homozygous sickle-cell anemia.[57] The absence of anemia found in many children reflects compensatory hyperactivity of the bone marrow and is indicated by an increased reticulocyte level. Sickle

cells are few or absent in the blood smear, but rapid and complete sickling occurs in sealed fresh preparations. Target cells are numerous, averaging 60 per cent (40 to 85 per cent). This feature is of some significance since excessive numbers of target cells in the blood smear of a patient with a mild form of sickle-cell anemia should arouse suspicion of the coexistence of hemoglobin C.

In this disorder in which the patient is heterozygous for both abnormal hemoglobins each of the components may be regarded as equally divided,[58] although hemoglobin C may range from 37 to 67 per cent. Fetal hemoglobin has been found in amounts up to 7 per cent. Transfusions may be required in episodes of severe hemolytic anemia, and splenectomy has been employed in some of the cases in which splenic infarction developed during flight.[59]

Sickle - Cell - Spherocytosis.—Sicklemia in combination with congenital spherocytosis has been observed with improvement of the anemia following splenectomy. Sickling remained unaffected with a residual blood pattern showing the sickle-cell trait (hemoglobins A-S). Each of the constitutional red cell defects (spherocytes and sickling) could be traced to individual parents.[60]

Sickle-Cell-Hemoglobin D Disease.—The patients are white persons in whom the coexistence of S and D hemoglobins results in a moderately severe hemolytic process similar to sickle-cell anemia. However, one parent reveals the sickle-cell trait, the other the trait of hemoglobin D. The blood count shows a moderate anemia of about 8 to 9 grams of hemoglobin per 100 ml. blood and a red count of approximately 2.5 million. The peripheral blood may show poikilocytosis, anisocytosis, polychromasia and occasional nucleated red cells. In two reported cases[15] the red cells were increased in size. A few partially sickled cells are found in the fixed smear. With sickling tests the holly leaf or slow variety of sickling occurs rather than the filamentous or rapid variety found in classical sickle-cell anemia. Target cells are infrequent. Up to 12 per cent fetal hemoglobin has been found. The liver and spleen may not be palpable or both organs may be greatly enlarged.

THALASSEMIA VARIANTS

Thalassemia-Hemoglobin C Disease.—This disease usually occurs in Negroes, exceptionally in white persons. The anemia varies in intensity; it may be mild, rarely severe—in which case a hemoglobin of 7 to 9.5 grams is observed. In the latter instance it runs the course of a severe, chronic, hypochromic, microcytic anemia although milder than in the homozygous thalassemia disease. Usually, however, there is no anemia and reticulocyte counts are not elevated. Osmotic fragility may be normal, but in a few cases increased resistance to hypotonic saline has been noted. The blood smear shows many target cells (20 to 60 per cent), anisocytosis and poikilocytosis, and an appreciable number of microspherocytes.[61, 62] Since the percentage of target cells in severe Cooley's anemia is usually less than 10 per cent, the finding of an unusually large percentage of these cells should lead one to suspect a hemoglobin variant of this disease. Reticulocytes number 2 to 5 per cent. Fetal hemoglobin is not elevated. Hepatosplenomegaly is either absent or moderate. The disease results from

the interaction of the genes for sickling and thalassemia inherited from respective parents bearing the trait. In this combination also the abnormal hemoglobin is present in an amount greatly in excess of that found in the parent and reflects the effect of coexistence with the thalassemia gene.

Thalassemia-Hemoglobin E Disease.—This represents a severe hemolytic syndrome simulating advanced Cooley's anemia (thalassemia major) so closely as to be indistinguishable from it except that the course may be somewhat milder. Most cases of the combined disease have their onset in infancy, although medical attention

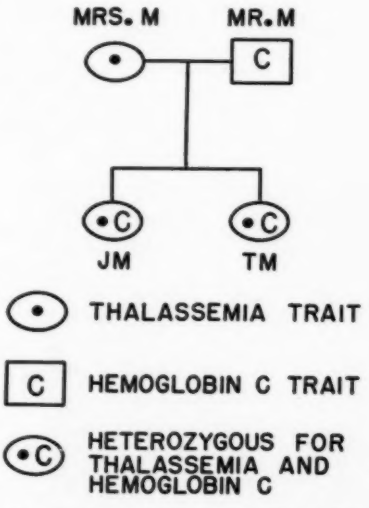

Fig. 5.—Example of a family pedigree, showing genetic transmission of double heterozygosity for two different sets of genes—thalassemia and hemoglobin C. (Based on the paper by Erlandson, M., Smith, C. H., and Schulman, I.: Pediatrics **17**: 740, 1956.)

may not be sought until adolescence. Fatigue, dyspnea on effort, joint pains, pallor, and jaundice occur frequently. The abdomen is markedly protuberant, the extremities are wasted, and jaundice varies in severity. Splenomegaly may be massive and hepatomegaly is less marked. The patients are of small stature and present a facial appearance with mongoloid features similar to those in classical Mediterranean anemia.

Hematologic examination reveals a microcytic, hypochromic, hemolytic anemia, with markedly lowered hemoglobin and red cell values. Reticulocyte counts are elevated. The blood smear coincides with that of the correspondingly severe Cooley's anemia. In some patients the stained blood smear reveals target cells, numbering 5 to 20 per cent of the red cells, and a small number of spherocytes. While osmotic fragility starts in more concentrated solutions of sodium chloride than is normal, fragility is not complete until the lowest dilutions are reached. Nucleated cells are prominent in the blood smear. The bone marrow as in Cooley's anemia shows marked erythrocytic hyperplasia. Hemoglobin analysis shows a mixture of hemoglobins E and F, with the former comprising 60 to 80 per cent of the total and fetal hemoglobin the remainder. Where complete studies have been available one parent possessed hemoglobin E, the other showed hematologic evidences of the thalassemia trait.

Transfusions are necessary in many of the younger children but for the entire group they are not as urgent as in severe Cooley's anemia. Splenectomy in many of these patients has been of benefit in promoting growth and better general health.

Variants of thalassemia with G and H hemoglobins have been described in other sections.

SUMMARY

To the extended list of hemoglobins enumerated in this review, there is

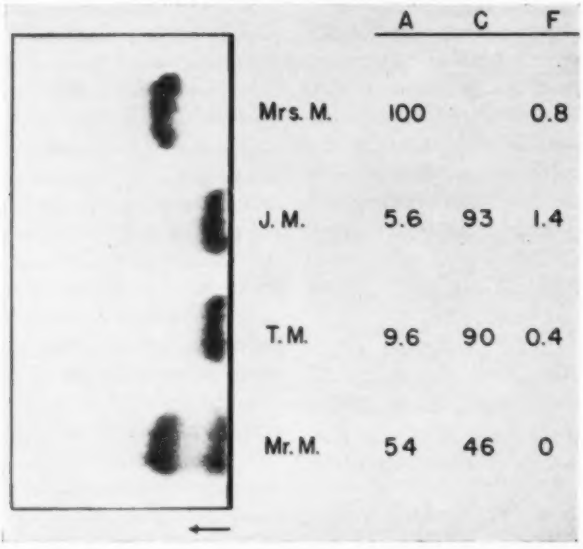

Fig. 6.—Paper electrophoresis of the M family (Fig. 5). Amounts of hemoglobins A and C are recorded as per cent. F = per cent fetal hemoglobin by alkali denaturation. It will be noted that both parents possess substantial amounts of normal hemoglobin (A). Apparently the simultaneous presence of the thalassemia gene appears to suppress hemoglobin A synthesis with augmented expressivity of the abnormal hemoglobin, in this case C hemoglobin. (Based on the paper by Erlandson, M., Smith, C. H., and Schulman, I.: Pediatrics 17: 740, 1956.)

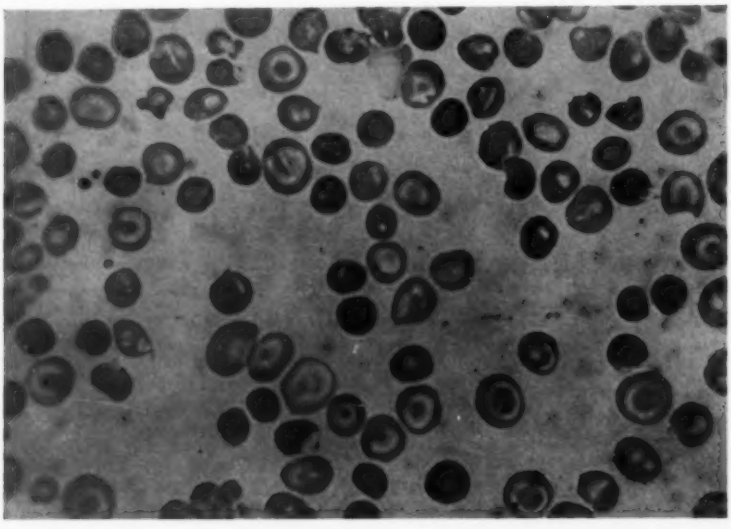

Fig. 7.—Photomicrograph of blood smear of a child with thalassemia-hemoglobin C disease (J. M. in Fig. 5). Note the presence of numerous dense microspherocytes and of target cells. (Based on the paper by Erlandson, M., Smith, C. H., and Schuman, I.: Pediatrics 17: 740, 1956.)

the almost certain likelihood of future supplementation by newer members. Thalassemia, for example, awaits the discovery of a specific hemoglobin or related compound as judged by its behavior in combination with other hemoglobins. The extraordinary phenomenon of the retardation of the synthesis of normal hemoglobin by the gene for thalassemia with the elaboration of fetal hemoglobin, and its potentiating effect on the synthesis of abnormal hemoglobins such as S, C, and F render this a plausible hypothesis.

While the large number of abnormal hemoglobins are important from many viewpoints, relatively few engage the interest of the practitioner in any particular locality. In the eastern part of this country, for instance, the hemoglobins most frequently encountered are those involved in sickle-cell disease, thalassemia (for the fetal hemoglobin content in the severe disease), or in combination with each other or with hemoglobin C. Also while few instances of hemoglobin E have been found in the United States, it is present in many native Thais but absent in pure Chinese living in Thailand.[18] The population composition in each geographic area necessitates, therefore, familiarity with specific types, not alone for their significant anthropologic connotation but for the diagnosis and management of indigenous anemias.

Knowledge in many related fields has been enriched by the investigation of the hereditary hemoglobinopathies. The biochemistry and physical behavior of the hemoglobins, their distribution throughout the world, and the quantitative aspects of genetic transmission factors which modify hemoglobin structure have provided information of basic importance beyond the immediate reference to the diseases which they influence.

Finally, these studies have permitted an assessment of the forces involved in establishing hematopoietic equilibrium in the hemolytic anemias. One of the most striking features in this group is the capacity of the bone marrow to respond by intensified rates of hemoglobin and red cell production in states of excessive hemolysis so that anemia is averted. This concept of compensated hemolytic disease is of fundamental importance in the interpretation of the clinical and hematologic vicissitudes of patients suffering from blood disorders in which decreased longevity of the red cells is an outstanding feature.

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Pediatric Profiles

Pediatrics in Vienna at the Beginning of the Century

Béla Schick

IF A person lives long enough, one of the advantages he enjoys is his collection of memories, his friendly relationship with the people he has met, including many of the leading members of his profession.

I lived in Europe forty-six years before I came to the United States in 1923. After graduating from the University in Graz in 1900, I served one year in the clinic of internal medicine of Friedrich Kraus and four months in the psychiatric clinic of Professor Anton. Following this I entered the pediatric department of Theodor Escherich. In 1901 Escherich was appointed to the pediatric chair of the University of Vienna. I joined his staff in January, 1902.

Escherich was young, distinguished-looking, and wore an impressive beard. This was not unusual at that time. In the United States Koplik wore a similar beard. Escherich was a representative of the era that believed that gastrointestinal disorders in infancy were caused by bacteria. He certainly deserves credit for realizing how important a role bacteria play in these disorders. He started his research with the discovery of the bacterium coli, which bears his name. He sensed the existence of different strains. He demonstrated that this normal inhabitant of the intestinal tract could become pathogenic and virulent. He also made the important observation that cystitis can originate from an infection with the colon bacillus. He furthermore considered the possibility that colitis and sepsis might be due to a colon bacillus of a different type, more aggressive and more potent. His clinic soon became a mecca for pediatricians, who were fascinated by the new bacteriological approach to pediatric problems. It was natural that Escherich should become interested in other bacteria, particularly in the diphtheria bacillus. He readily accepted O'Dwyer's intubation method. He also studied streptococci and

staphylococci. The diagnostic use of tuberculin, originated by Koch, interested him. He and Epstein discovered the Stich reaction to tuberculin. This was an inflammatory reaction at the site of the injection of tuberculin whereas Koch's reaction was a febrile reaction. The Stich reaction was a skin reaction like the Pirquet and Mantoux reaction. Neither Escherich nor Epstein realized the great practical and diagnostic value of the Stich reaction.

Escherich's preoccupation with the colon bacillus stood in his way of making another important discovery. When he cultured colon bacilli from the gastrointestinal tract, he focused his attention on the gram-negative strains which produced gas in the agar-culture medium and discarded those strains which did not produce gas. This discarded bacillus was the dysentery bacillus later described by Flexner.

As long as Escherich lived, the bacterial flora of the gastrointestinal tract was his favorite topic of study. Rach and Jehle, assistants of the Viennese clinic, were devoting their time to this difficult problem. Frequently, when a foreign student came to the clinic eager to study a problem, Escherich would suggest his pet subject.

Escherich was an excellent organizer and fully recognized the importance of new discoveries. For a long time he was interested in tetany. Kassowitz called tetany only a nervous disorder of rickets. Escherich fought for the conception that it was a disease independent of rickets. He was exceedingly impressed by the study of Erdheim which proved the connection of tetany with the function of the parathyroid gland. A Japanese physician, Yanase, whom Escherich put to work on this problem, published an excellent study on this subject.

In Escherich's time, the advantages of breast milk over cow's milk were in the foreground of pediatric discussions. The inauguration of social welfare organizations for the protection of infants and children (Kinderschutz and Säuglingsfürsorge) was close to Escherich's heart. His personal charm enabled him to interest some of the well-to-do people of Vienna, and so he succeeded in raising money to carry out his plan of free milk distribution to infants. In this way he participated in the education of physicians and mothers in hygiene and other phases of child care. The high infant mortality could not fail to be a challenge to the profession. Escherich was not alone in his fight against this high mortality. All over Europe, particularly in France and Germany, the problem was the center of attention. At pediatric meetings the first two days were devoted to feeding and gastrointestinal problems. Other problems were postponed to the succeeding days, when the speakers usually talked to empty seats, many of the members having left for home.

The bacterial era inaugurated in pediatrics by Escherich was preceded by a period when gastrointestinal disorders were explained on the basis of pathology. This was the effect of the brilliant teaching and fundamental discoveries of Rokitansky. He dominated medical thinking in Austria. It was he who was responsible for the passage of a most important law which originated in the famous "Allgemeines Krankenhaus" in Vienna, providing that every patient who died in the hospital must be autopsied. There is

no doubt that much of the progress in clinical medicine was a result of this law. Careful clinical observation and diagnosis were encouraged, because the correctness of clinical observations was subject to confirmation by autopsy findings. These findings afforded a means of judging the diagnostic ability of the leading physicians. In this way, too, the hospital staff learned of clinical errors.

The leading pediatrician of Vienna who represented the concept of a pathologic basis of gastrointestinal disorders was Escherich's predecessor, Professor Widerhofer. He described pathologic findings, inflammatory and destructive, in the intestinal tract. His teaching classified gastrointestinal disorders as a catarrhal condition, or as gastroenteritis with or without ulcerations. The ending "itis" meant inflammatory findings. Later studies have proved that dysenteric infection was apparently responsible for the findings. Pathology alone could not solve the riddle of acute and chronic diarrheic conditions. Contrary to expectation it was extremely disappointing how little the study of gross pathology and histology could offer. Since the fundamental damage could not be seen, the pathologist was not eager to autopsy such infants, as he disliked reporting negative results.

Science cannot afford to stand still. New ways had to be developed to study the pathogenesis of gastrointestinal disorders of infants.

Peculiarly enough, Widerhofer, the pediatrician, was also the personal physician of the Emperor Franz Josef I. Having a pediatrician in such a high position was very helpful for pediatrics in Vienna. It may be that pediatrics and geriatrics have more in common than we realize.

The high infant mortality was mostly due to gastrointestinal disorders. It was higher in bottle-fed children than in the breast fed. Obstetricians differed in their attitude but the pediatrician fought for breast feeding, since it gave a certain guarantee for better development of the infant. Most of the mothers in Vienna were rather fond of the idea of nursing their children. Of course some were really unable to nurse their children, but many refused nursing due to their fear of becoming stout, of breast enlargement, of painful abscesses, etc.

Moll contended that mothers who did not want to nurse their children used the lack of milk as an excuse. For a while Aristocracy and Royalty set a good example by nursing their infants. Even today many pediatricians in Europe state that premature children can be raised only with breast milk. Czerny used to say: "Breast milk will almost always be well tolerated." It must be pointed out that breast milk has some important advantages, for example, the transmission of useful ferments and antibodies.

In attempting to explain the difficulty of using cow's milk for feeding infants, its chemical composition was blamed. Cow's milk contains double the amount of protein, more minerals, and less sugar. The greater amount of protein was considered to be the main offender. Biedert spoke of the difficulty of digesting casein. His forceful personality influenced many pediatricians, but not Escherich, who told me that he himself was an autodidact, and therefore remained unaffected by the teachings of Biedert in spite of the fact that he was a

pupil of his. Many years have gone by, and although Biedert's theory has, to a great extent, been abandoned, dilutions of cow's milk and soft curdled milk are procedures that still survive.

For a short period of time predigested cow's milk (called Backhaus milk) was used in Vienna. The predigestion was made with pancreatic ferment. The manufacture of substitutes for breast milk led to innumerable milk modifications. The chemical composition of these modifications was always claimed to be similar to the composition of breast milk. Even at present certain proprietary milks have the same foundation.

At the same time as these chemical ideas were being discussed, serology came into prominence. It proved that every protein is specific; i.e., cow's milk protein can never be converted into human protein. The "Arteigenheit" of the protein of every milk was given as an explanation for the difference in the results of breast and bottle feeding. This theory, originated by Hamburger, was a pessimistic one, as it offered no hope for the equalization of human and cow's milk. Fortunately it was shown that the digestion of both human and cow's milk protein leads to the same end product—amino acids. This theory of Hamburger was defeated by Kassowitz at a pediatric meeting.

At this meeting Kassowitz reported his excellent results obtained by feeding infants with cow's milk. He then declared that the whole problem of cow's milk versus breast feeding could be solved if the cow's milk would flow from the breast of the mother. I think Kassowitz hit the nail on the head; with his "classical remark" he put the problem in its right place. He realized that milk is an excellent culture medium for bacteria, and that only the totality of milk hygiene, starting with the cow and the stable up to the child, could remove the danger of using cow's milk for infant feeding. This would include cleanliness of handling the milk, refrigeration, pasteurization, etc. In Italy, where refrigeration was not widespread, goat's milk was frequently used; the goat was driven into the court of the house and milked there. The time consumed to get the milk to the child was minimal and the lack of refrigeration was therefore of less importance. All countries which have a high infant mortality on account of gastrointestinal disorders are certainly much better off with breast feeding. If breast feeding is to be replaced, dried or evaporated milk and refrigeration in the home are indicated. This would especially apply to semitropical and tropical countries where the higher temperature increases the danger of bacterial infection of the milk.

For many years, complicated milk formulas have been used in Europe and in the United States. We know now that such complicated formulas are not necessary. Two-thirds milk and one-third water, with an adequate addition of carbohydrate, is a simple and effective formula in the great majority of cases. Overfeeding and underfeeding must be avoided. Nature is very kind to the pediatrician and to the child, in that it gave the infant an excellent tolerance.

An interesting remark by Epstein (Prague) is worth mentioning. He said "Du kannst ein Kind mit Stroh ernähren nur kümmern musst du dich um ihn." This means that you can feed a child with straw, only you

must take good care of him. Epstein meant to lay emphasis upon the importance of the use of psychology in the raising of infants—motherly love, and a happy and cheerful environment for the child. Finkelstein remarked that an infant sometimes does not thrive in the hospital. When the same infant is given special care by an excellent nurse who substitutes the warmth and love of the real mother, he will thrive. Surely all of us have had this experience.

At the beginning of this century, pediatrics in Vienna, so far as infants were concerned, was very much under the influence of German pediatricians. But we in Vienna were always interested in diseases of older children, in infectious diseases, particularly scarlet fever, diphtheria, and measles. We did not like to be considered only baby-feeders, a specialty which internists would have liked to relegate us. We always fight against the idea that children's diseases beyond infancy are not different from internal diseases of adults. Children are not simply micro-adults, but have their own specific problems. At this time many hospitals were built in Germany only for infants (Säuglingsheime and Säuglingsspitäler). In Germany great rivalry existed between the school of Finkelstein and that of Czerny. But in Vienna there was no dissention between us of the Escherich and Pirquet school and the other Viennese pediatricians such as Knoepfelmacher, Moll, etc. We felt that there was room for all. We were too busy in the hospital where almost everybody worked in the wards and outpatient department up to lunch time. Immediately after lunch we all rushed by streetcar to the Serotherapeutical Institute, where Paltauf and Rudolf Kraus worked. This institute was our laboratory. We had none in the clinic for several years.

Knoepfelmacher was an excellent clinician, teacher, and a well-known consultant. He attracted many American physicians who went to Vienna to study under him. A victim of the Hitler terror, he had a tragic end. In 1938 he was returning to Austria from Czechoslovakia, when customs officials at the frontier took away his passport. These were terrifying times and he became so nervous and frightened that he attempted to commit suicide by means of morphine. The dose being insufficient, he lived for several days and then succumbed to a complicating pneumonia.

Kassowitz and Hochsinger had their own dispensary in the "Steindlgasse." Kassowitz was an interesting character, highly educated, and a fine thinker. He was very critical in accepting diphtheria antitoxin discovered by Behring. But he was absolutely honest in his opposition, particularly attacking the statistical proof of the results of serotherapy. Although he insisted in his opposition for a long time, he nevertheless used the serum in his practice. Not until I could demonstrate that immunity and susceptibility could be determined by my test did he admit that diphtheria antitoxin was valuable.

Kassowitz treated rickets with phosphor-cod-liver oil, but he erred when he stated that the phosphorus was the principal factor. We know that it was a lucky chance that led him to choose cod-liver oil as a solvent. His reputation among the laity was so great that the people streamed to the "Steindlgasse" to procure the miracu-

lous medicine. In spite of the fact that the same kind of cod-liver oil was dispensed all over Vienna, the people believed that the cod-liver oil of the Steindlgasse was better and more effective. Hochsinger, Kassowitz' colleague, was known for his study of syphilis.

Moll became the director of the beautiful "Reichsanstalt für Mutterschutz und Kinderfürsorge," where he carried on important studies of nutrition of infants. Here he established an excellent school for nurses, educating them for home care and public health. His institute received the nickname "Molloseum."

Upon my arrival at the clinic in Vienna in January, 1902, there was great excitement. Moser, the first assistant of Widerhofer who had been taken over by Escherich, had just accomplished his startling development of an effective, specific antistreptococcus serum against scarlet fever. I also became very enthusiastic when I saw the astounding effect of this Moser serum upon children desperately sick and almost dying from scarlet fever. Six to eight hours after injection of the serum the temperature started to fall, and the next morning the child was sitting up in bed, taking breakfast. Consequently the whole clinic looked up to Moser with great admiration. The effect of the serum was more dramatic than the effect of diphtheria serum upon diphtheria. I was fortunate enough to be immediately assigned to the scarlet fever pavilion as a volunteer or "aspirant." My immediate superior and attending physician was Pirquet.

I still cannot understand why this outstanding discovery of Moser did not receive due recognition and was even attacked. Only Russian physicians shared the clinic's enthusiasm for the Moser serum. Apparently they were in dire need of the serum since they were called upon to cope with violent epidemics of scarlet fever. Moser obtained his specific streptococci from the heart blood of fatal scarlet fever cases. By repeated injections of the living streptococci into horses the serum obtained agglutinated the streptococci specifically. There was no method to prove the efficiency of the serum other than the treatment of scarlet fever patients. Typing of streptococci was not yet known. Not every horse produced an effective serum, a fact which applies also in the preparation of diphtheria antitoxin. This militated against the acceptance of the serum. The passing of twenty-five years was necessary before Moser's discovery, meanwhile almost forgotten, was revived by the Dicks and Dochez. That Moser started with small doses of his serum interested me. Only the incredible acuity of Moser's clinical observation that a larger amount of serum had an increasingly better influence upon scarlet fever was responsible for his continuing the treatment with larger doses. The final dose was the enormous amount of 180 to 200 c.c. It required courage to use this large amount. In some cases intensive serum sickness developed and this gave Pirquet and me the opportunity to study this disease, and Pirquet the basis for his great discovery of allergy. I spent five years of my life in the scarlet fever pavilion of the old St. Anna-Spital and became the successor of Pirquet in the scarlet fever ward. This was a fortunate turn of events, en-

abling me to write a monograph dealing with scarlet fever for the Nothnagel Handbook of Medicine.

This period of pediatrics in Vienna was an exciting one. In those days Vienna had acquired a cultural leadership which gave it a foremost place among European cities. It was known for all forms of intellectual development, artistic and musical as well as scientific. To this period belongs Pirquet's great discovery of allergy.

The first observation was made by Pirquet on December 2, 1902, in a patient named Egon H. The child, suffering from scarlet fever, had received 100 c.c. Moser scarlet fever serum on October 13, 1902. After an incubation time of seven days, serum sickness started and lasted several weeks. Fifty days after the first injection the child was reinjected with 2 c.c. of diphtheria serum because a diphtheria case was discovered on the ward. Fifteen minutes after the injection the child vomited and developed edema of the lips which rapidly spread over the face. A few hours later a general urticaria eruption appeared. The observation that this second injection was followed immediately by a serum reaction constituted the starting point of Pirquet's study of serum sickness, in which I collaborated and which led finally to the coining of a new term—allergy. The term was published by Pirquet in 1906, just fifty years ago.* The year 1956 is therefore the fiftieth anniversary of the discovery of allergy. The importance of this discovery is so well known that it is not necessary to discuss it in detail.

We know that tuberculin testing, as well as other skin testing, is the direct result of this discovery. The "Serum Sickness" was published in 1905, became a classic, and was finally translated into English in 1951. Two important studies of Pirquet concerning smallpox vaccination and measles followed. The pathogenesis of a large group of diseases, among them hay fever, asthma, eczema, and urticaria, became clearer. Every day other diseases such as rheumatic infection, nephritis, and collagen diseases were shown to have allergic features. Lately periarteritis nodosa and lupus erythematosis are claimed to be allergic in nature. The problem of immunity was studied with allergy as its basis. Pirquet realized the importance of allergy and all its ramifications, involving many infectious diseases, particularly tuberculosis. It was a discovery which revolutionized not only pediatrics but all medical science. The term allergy became a word in the layman's vocabulary.

The fame of Pirquet spread over the whole world upon the discovery of his tuberculin test which became, together with x-rays, the main weapon in the study and fight against tuberculosis. The greatness of the discovery of allergy was realized in the United States. In 1908 Pirquet was called to this country to occupy the chair of Pediatrics at the Johns Hopkins University in Baltimore. He was a real genius. As a collaborater and friend, I can better measure his greatness than most other people.

I know how he influenced my own research work. My association with him had much to do with the discovery

*A reviewer, whose name I do not remember, found it appropriate to state that Pirquet's paper was not important and was a superfluous publication introducing a new and useless term. I hope that the reviewer has meanwhile learned what a great mistake he made.

of my diphtheria test. I met Pirquet for the first time when I was a medical student in Graz. The number of students in the class was very small (about thirty), so that we all knew each other at least by sight. The department of internal medicine had no auditorium; we sat on chairs around our teacher Friedrich Kraus, literally at his feet. I realize what an advantage we students had to be so close to our great teachers. Pirquet was always with his friend Haberer, who later became an outstanding surgeon. Both were always the first to be ready for the examinations and therefore the first of our group to be graduated. Born in Belgium, Pirquet received an excellent education. It is interesting to note that before becoming a medical student, he studied for the priesthood. Besides German, he spoke English, French, and Italian fluently like a native of the respective countries. He was a born leader in international affairs. It should be mentioned that at one time he and Wagner-Jauregg, professor of psychiatry, were considered for the presidency of Austria. Concerning this proposition, humoristic remarks were made. It was said that Austria was so childish that a pediatrician was best fit for the presidency, or that Austria was in a dangerous mental condition needing a psychiatrist. The situation in Germany after the First World War as compared with Austria was summed up in the statement that while the conditions in Germany were serious but not hopeless, those in Austria were hopeless but not serious.

Two other assistants of the clinic should be mentioned, namely, Jehle and Reuss. Jehle was very much occupied with the problem of "lordotic albuminuria." He really coined this term as he proved that the so-called orthostatic albuminuria was due to a lordotic posture of an individual. The spinal column at a certain level exerted pressure upon the vessels of the kidneys. His discovery was made when he observed that his niece had albumin in her urine when she played the violin. The albumin disappeared when she was sitting or leaning over the table with a straight spinal column. He further found that children in the wards who had orthostatic albuminuria had more than usual albumin on Sundays after attending church services where they had to kneel and persist in this position. By a very simple experiment, producing lordosis, Jehle was able to prove the correctness of his explanation. This splendid work is not sufficiently appreciated. An excellent article about lordotic albuminuria appeared in the *Ergebnisse der inneren Medicin und Kinderheilkunde*, in 1913, the first and shorter publication in the *Münchener medizinische Wochenschrift*, in 1908.

Dr. Reuss, another assistant at the clinic, had worked at the Hofmeister Institute in Strassburg, and had therefore obtained an excellent education in chemistry. In Vienna he became interested in the newborn. Escherich selected him as attending pediatrician at the obstetrical clinic of Prof. Schauta. This newborn station became the first station to have a pediatric chief. The studies carried on by Dr. Reuss were very interesting and led to the publication of a classical book about the newborn, which became known all over the world. I succeeded Reuss as pediatrician in the newborn service during the First World War and had the opportunity of studying

many problems of the newborn period, such as icterus neonatorum, nutrition of the newborn, food requirement of mothers during pregnancy and of nursing mothers. Reuss later became professor of pediatrics in Graz, then successor of Moll as director of the Reichsanstalt für Mutterschutz and Säuglingsfürsorge, and finally professor of pediatrics in Vienna following Hamburger. It is interesting that Reuss was the best amateur violin and viola player in Vienna. For a while he wanted to be a professional musician and join the Philharmonic Orchestra of Vienna.

Zappert and Neurath were outstanding pediatricians but not directly connected with the University clinic. They were particularly interested in neurological problems and published many valuable contributions to this subject.

Leiner was an outstanding pediatric dermatologist, accepted by dermatologists as one of their members. He and Lehndorff were active in Knoepfelmacher's hospital. Lehndorff studied hematology, in which field he became well known.

In those days the Vienna Clinic was certainly an excellent place to do research work. The clinic was housed in the Sanct Anna Kinderspital, one of the oldest children's hospitals in Europe. It was founded and supported by private charity, the contributors being mostly aristocrats. We had excellent nurses who were Catholic nuns. The State subsidized the hospital, appointing and paying the salary of the director who was the official professor of pediatrics of the University. Two of the assistants were also paid, and later a third was added to the paid staff, but the rest were unpaid assistants and volunteers. There was a small auditorium for teaching the students. The interns were paid by the hospital but were selected by the professor. The facilities were very limited, the wards were rather dark, and the dispensary lacked sufficient waiting rooms, light, and water. But the spirit was high and this hospital was one of the few hospitals that admitted children, particularly children below 4 years of age, who were otherwise entirely forgotten. This was apparently due to the prevailing opinion that children below 4 years and infants should be under the care of their mothers and not in a hospital. Escherich tried to open an infants' ward in the old hospital, with tragic results. All children, even the baby of the wet nurse, died in a short time. Escherich spent much effort in an attempt to organize the infants' ward, but he realized that the only solution was a new State-supported pediatric clinic. Eight years after his arrival in Vienna, Escherich succeeded in convincing the State to erect a new clinic, which was done partly with the money of the old Sanct Anna Kinderspital. At the entrance of the new clinic the name "Sanct Anna Kinderspital" was affixed, the only sign of the contribution of the old hospital. There were magnificent plans for the new clinic. Completed in 1911, the new clinic became known as one of the best hospitals for children. It was tragic that Escherich never saw his dream clinic.

The first symptom of the impending disaster was that Escherich started to talk French at the rounds and complained of headache. He died suddenly several days afterward, apparently from a cerebral hemorrhage. The whole clinic was shocked, depressed, and felt like a family which had lost

its father. The future of the members of the staff was uncertain. Everything depended upon the decision: Who will be the new chief. After many months of indecision Pirquet was called from Breslau and appointed as Escherich's successor. Under his leadership, the pediatric department rose to new heights and attained fame for the extensive and interesting work conducted within its walls. This decision was particularly fortunate for me, because Pirquet selected me as his first assistant.

A peculiar episode I wish to relate. All assistants of the clinic were taken by the new department. The interns and the patients remained in the old hospital. The numerous dispensary patients had been advised for many months that the new clinic would open in October, 1911. For days before our departure we praised the beautiful rooms and other advantages that the new hospital would have over the old. We impressed the parents of our dispensary patients with the fact that all of us would be no longer in the old dispensary. The patients and parents would find us in the new clinic. They asserted that they did not wish to be treated by any other doctor, they were loyal to us and would come to the new clinic.

We felt certain that they would keep their promise and we were flattered by the statement. During the days just preceding our departure from the old hospital we renewed our invitation to the patients to come to the new building. The transportation offered no difficulties since the same streetcar went to the clinic only one stop further.

On the opening day of the new quarters we experienced a great disappointment. We did not see any of our old patients, nor did any other patient show up. Finally I went over to the old hospital and to my great surprise I saw all my patients and the patients of our other assistents sitting in their accustomed places. Disturbed by this turn of events I personally took about twenty of my patients over to the new clinic, marching at the head of the column.

From this experience I learned, and wish to impress upon my colleagues, not to be conceited and to realize that the well-known walls of an old building play a great role with the patients. The confidence they profess to have in their physician must not be taken too seriously.

We were happy with our new leader. Pirquet's personality, his character, and his active brain influenced my whole life and everybody around him.

Pirquet's love for truth, his respect for and understanding of his fellow man, his liberalism, his joy in helping others, his complete lack of envy or jealousy made everybody around him better human beings. It prevented anybody from approaching him with unworthy motives. Only once did I see him angry and this was during the Austrian revolution after the First World War, when officials of the government mistreated members of the medical faculty, whereas the revolutionary forces were treated with the softest kind of gloves. Employees of the hospital, including the washer- and scrubwomen, were all considered more important than the physicians.

Pirquet never wanted to listen to derogatory remarks made by one staff member about another. Such comments were taboo. All members of the staff worked quietly on their respective problems. There were no fractions within the staff. We all were busy concentrating our efforts on building up a children's department that would be respected by the pediatric world and by ourselves. Life

in the clinic was peaceful. Pirquet brought new ideas into the clinic. Everybody was eager to do his part toward developing the department. Among the members of the staff, Raeh, Koeh, Nobel, Wagner, Mayerhofer, and Wimberger became outstanding pediatricians. Nobel and Mayerhofer were active in organizing the work of the American relief administration of Hoover. Wagner studied diabetes in childhood and with Priesel, published a classical study of this disease. Wagner is now connected with the pediatric department of Tufts University in Boston. Raeh and Wimberger specialized in roentgenology, Koeh in tuberculosis. Mayerhofer became professor of pediatrics at the new university in Zagreb. Pirquet tried to make everybody happy. The children were taught to greet him at grand rounds with the typical Viennese "Grüss Gott" (God greet you). The same welcome was given whenever a guest entered a ward. We had established a department for about one hundred tubercular patients on the roof, where we introduced heliotherapy and open-air treatment. They had their school, the certificate of which was accepted by the regular schools. Entertainment, play, and recreation were planned. The children learned songs. Pirquet, remembering his happy days in Baltimore, taught the children to sing not only Viennese and German songs, but also American songs as, for example, "My Old Kentucky Home" and "The Old Folks at Home." We had many visitors from the United States who enjoyed the songs. One can imagine how happy American visitors were hearing American songs in Vienna. Birthday parties and Christmas celebrations gave children the opportunity to show their theatrical ability. Pirquet and Mrs. Pirquet came to many of these festivals, and at masquerade parties he liked to appear in Chinese costumes, singing Chinese songs. Already as a young assistant he played with the patients in the ward. He told excellent fairy tales which he himself invented.

The First World War started in 1914 and did not interrupt the intensive constructive work in the clinic. But after the war the situation of Austria became desperate. The organization of the Relief Administration of the Hoover action led to plenty of interesting studies on nutrition and the vitamins. The conquest of rickets and scurvy and of other avitaminoses was accomplished. But the whole situation deteriorated not only politically, but it harmed the possibility of scientific research in the University. It is understandable that Pirquet realized the desperate situation of Austria. He saw no hope for the near future. This may have contributed to his tragic decision to commit suicide. Pediatrics lost one of its greatest leaders.

The present professor of pediatrics in Vienna, Dr. Karl Kundratitz, is working hard to revitalize the famous Vienna Kinderklinik.

Béla Schick.

Comments on Current Literature

HUMAN SALIVARY GLAND VIRUS (SGV)

INTRANUCLEAR inclusion bodies resembling those described in the salivary glands of several species of rodents have been observed in the salivary glands of infants and children, being reported in from 10 to 30 per cent of autopsies performed, irrespective of the cause of death, and without apparent connection with active virus infection. In recent years a systemic infection designated as cytomegalic inclusion disease has been described which is characterized by the presence of intranuclear inclusions in enlarged cells of many viscera. Cytomegalic inclusion disease is thought to represent a generalized or systemic manifestation of the salivary gland virus type of infection. The most typical clinical pattern of the disease occurs during the newborn period with hepatomegaly, splenomegaly, jaundice, anemia, thrombocytopenia, and purpura. Severe cerebral damage with associated cerebral calcification has been reported.[1] Calcification in the brain as a manifestation of inclusion body disease was emphasized recently by Sackett and Ford[2] in a case report appearing in the *American Journal of Roentgenology* (September, 1956). This was the case of a newborn infant with cytomegalic inclusion disease who was admitted to the hospital on the first day of life because of jaundice, petechiae, and hepatosplenomegaly, and who survived for a period of ninety days. Roentgenograms of the skull showed marked microcephaly, overriding of the bones of the calvarium, and a layer of calcification outlining the dilated lateral ventricles.

While for some time the infectious agent responsible for this disease has been considered to be a virus, transfer of the human disease agent to experimental animals proved difficult. However, the species-specific virus of mouse salivary gland disease was cultured successfully in mouse tissue culture, and has been propagated by serial passage.[3] Recently a viral agent was incriminated specifically in the human infection, virus having been isolated from salivary gland tissue, where these glands were involved, and from various tissues of the body where there was cytomegalic inclusion disease with general involvement. In the June, 1956, issue of the *Proceedings of the Society for Experimental Biology and Medicine*, two articles appear which throw considerable light on the subject of human infection with salivary gland virus. One of these, a further report by Margaret G. Smith,[4] describes the isolation of a viral agent from submaxillary salivary gland tissue taken at the time of autopsy from a 7-month-old infant whose death resulted from adrenal cortical carcinoma. A similar viral agent was obtained from kidney tissue taken at autopsy from an infant one month of age who had signs and symptoms of generalized cytomegalic inclusion disease. "Many characteristic inclusions were present in microsections of the kidneys and other viscera, as well as in the salivary glands of this infant."[4] These agents produced cytopathologic changes in human cell tissue culture—fibroblasts derived originally from human uterine tissue. Large intranuclear inclusions were observed in the enlarged rounded

cells of infected cultures. Successive serial passages of these viral agents in tissue culture were accomplished readily, and neutralization tests employing human sera indicated that antibodies from human subjects neutralize the cytopathogenic effect of the virus strains. The first strain obtained from the submaxillary salivary gland of an infant dying of adrenal cortical carcinoma was neutralized by serum specimens from two infants who died in the newborn period of generalized cytomegalic inclusion disease, and by serum from the mother of one of these infants, the serum specimen in the case of the mother being obtained one month following the infant's birth. All experimental studies have indicated that these two newly isolated viral agents are species-specific for the human subject, and all observations have pointed to the conclusion that the two strains of virus are similar, one isolated from the salivary gland, and one from the kidney of a patient with generalized cytomegalic inclusion disease.

In the same issue of the Meltzer Society journal, Rowe, Huebner, and their associates[5] report the isolation of a cytopathogenic agent resembling human salivary gland virus which was recovered from human adenoid tissue (surgical specimens) undergoing spontaneous degeneration in tissue culture. These authors make reference to the isolation by Weller[6] (unpublished investigations) of a strain of human salivary gland virus from liver biopsy tissue obtained from an infant who showed clinical manifestations of cytomegalic inclusion disease. The three strains of virus described by Rowe, Huebner, and their associates[5] produce intranuclear inclusion bodies and show similar cultural behavior. They were encountered in adenoid tissue cultures in which the fibroblasts were undergoing spontaneous degeneration. The original tissue source consisted of surgical specimens obtained from children admitted to the hospital for tonsillectomy-adenoidectomy: an 11-year-old boy, a 7-year-old girl, and a 6-year-old girl. These strains of salivary gland-like virus were recovered in the course of tissue culture studies designed to check for the occurrence of adenoidal-pharyngeal-conjunctival (APC) viruses in human adenoids. The three strains of virus were similar in behavior, producing cytopathogenic changes in all types of human fibroblast cultures, including tonsils, adenoids, and foreskin and embryonic skin-muscle tissue culture preparations. These agents were established readily in serial tissue culture passage. Immunologic studies showed that antibodies present in human serum were capable of neutralizing the cytopathogenic effect of these strains, and gave evidence that these viruses isolated from adenoid tissue had characteristics very similar to, if not identical with, the agents isolated by Smith and by Weller. In discussing the relationships between the various newly isolated strains, and the significance of the recent findings, the authors suggest that there may be only one serologic type of this agent, and that the virus might well persist in the body in much the same manner as in the case of herpes simplex. Since the virus has been demonstrated now in adenoid tissue, it is suggested also that the virus might persist in latent form in adenoid tissue, as well as in the salivary gland. The demonstration of type-specific antibodies in a high proportion of human serum specimens tested indicated possible wide distribution of this agent among members of the human population.

The etiological relationship between local asymptomatic tissue infection, such as that in salivary glands or adenoids, and generalized infection with attendant clinical manifestations, as in cytomegalic inclusion disease, is brought out clearly by these investigations, and constitutes a timely and important subject. Studies elucidating this relationship between silent virus infection in healthy human subjects and clinical manifestations of

disease are of interest also from the standpoint of the dynamic balance between host and parasite.

RUSSELL J. BLATTNER

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News and Notes

The following were certified by the **American Board of Pediatrics**, at the examination held in New York, October 12 to 14, 1956.

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Dr. Judith Lee Wood, 940 Pine St., Glenview, Ill.

Special Foreign Certificates

Dr. Purificacion M. Espinosa, 440 Pelaez St., Ext. Cebu City, Philippines.

Dr. Rolv Kjelberg Slungaard, Gundersen Clinic, La Crosse, Wis.

The following Special Foreign Certificate could not be listed previously. It is as follows:

Dr. Seeta Lall, c/o Mrs. R. N. Batra, Ivanhoe, Back Bay Rlc., Bombay, India.

The Board has issued the following regulations in regard to the selection of candidates for oral examination in 1957:

1. Candidate must have successfully passed a written examination.

2. Candidates will be called in the order in which their applications were received.

3. Candidates will not be called prior to their eligibility date. Therefore, *please do not choose a date prior to the same.*

4. Candidates should indicate a second choice as the list for each session must be filled.

5. ALTERNATES should also list a first and second choice and, so far as possible, these will be heeded.

6. Refusal of an appointment will not prejudice subsequent call but candidates are expected to accept an appointment within two years following successful completion of the written examination. This two-year period may be extended upon written request by the candidate for such period of time as the Board, in its sole discretion, deems advisable.

Oral examinations for 1957 have been scheduled as follows:

1. New Orleans, La., Feb. 22, 23, and 24, 1957.

2. Washington, D. C., April 4, 5, and 6, 1957.

3. San Francisco, Calif., June 21, 22, and 23, 1957.

4. Chicago, Ill., Oct. 11, 12, and 13, 1957.

5. Boston, Mass., Dec. 6, 7, and 8, 1957.

Candidates taking the 1957 written should make their choices for oral examination *now* and *not wait* until notice of result of written examination is received.

The **University of California Medical Center**, Los Angeles, is offering an extension course in "Disorders of Fluid and Electrolyte Metabolism, Etiology, and Management." The course is designed to present up-to-date and practical information of the diagnosis and treatment of disorders of water and electrolyte balance by highly competent clinicians where main interests lie in this field. The course will be held Tuesday nights, February 5 to March 26, 1957. Requests for applications or information should be made to Thomas H. Sternberg, M.D., Assistant Dean for Postgraduate Medical Education, University of California Medical Center, Los Angeles 24, Calif.

Dr. Leroy E. Burney, Surgeon General of the Public Health Service, has announced that awards of more than $700,000 for a four-year investigation into the causes of cerebral palsy and mental retardation have been made to Yale University School of Medicine and to Brown University. These mark the beginning of a large coordinated research program which, during the next ten to twenty years, will attempt to identify factors responsible for such disorders as cerebral palsy, mental retardation, blindness, and deafness. Brown and Yale Universities are the first of a dozen or more institutions that are expected to join in this research program. Yale's grant for the first year is $107,799; Brown University is receiving $97,633. The Surgeon General said plans contemplate that more than $1 million yearly will be awarded to medical institutions under the program of the National Institute of Neurological Diseases and Blindness.

The Committee of the **VIII International Congress of Paediatrics**, held at Copenhagen, Denmark, July 22 to 27, 1956, has the following Transactions available:

Exhibition Catalogue, 130 pages (published July, 1956) Danish kr. 15.00.

Abstracts of Papers, 148 pages (published July, 1956) Danish kr. 20.00.

Discussions, about 176 pages (will appear in November, 1956) Danish kr. 20.00.

Active members of the Congress will receive the book of discussions free. Others may obtain the complete set of books at a price of Danish kr. 50.00 by applying to: VIII International Congress of Paediatrics, c/o J. Vesterdal, M.D., University Clinic of Paediatrics, Rigshospitalet, Copenhagen, Denmark.

Books

Vergiftungen im Kindesalter. Prof. Dr. med. Herbert Brugsch, Stuttgart, 1956, Ferdinand Enke Verlag, 222 pages. Price 25.50 DM.

A text by Dr. Brugsch, chief of the pediatric department of the City Hospital, Berlin-Moabit. Most of the book discusses poisoning due to medicinal and chemical substances, with shorter chapters on poisoning from plants, fungi, and animal causes. The material is arranged alphabetically. Many begin with short case histories. This is followed by paragraphs devoted to symptomatology and therapy. Each is followed by an excellent, up-to-date bibliography which shows an extensive knowledge of world literature.

Speech Handicapped School Children, ed. rev. J. Johnson, S. F. Brown, J. F. Curtis, C. W. Edney, and J. Keaster, New York, 1956, Harper & Brothers, 575 pages. Price $4.50.

A completely revised edition of the text published in 1946.

Environment and the Deaf Child. Steven Getz, Ph.D., Springfield, Ill., 1956, Charles C Thomas, 173 pages. Price $3.75.

A reprinting of the text published in 1953.

Editor's Column

"HIBERNATION"

THE term "hibernation" is frequently encountered in current continental European medical literature, but we have rarely run across the word in pediatric journals published in English. In general, the term is used to include physical measures and drugs used to produce hypothermia which brings about a lowered metabolic rate. In addition, the drugs have a depressive action on the central and autonomic nervous systems.

A number of years ago, Fay, of Philadelphia, used physical methods to produce hypothermia for therapeutic purposes, but his ideas and methods did not gain general acceptance or use. A renewed interest in the physiologic effects of hypothermia took place during World War II in connection with aviation medicine. Not infrequently airplanes were downed over the English Channel and North Sea, and the aviators exposed to long immersion in water at extremely low temperatures. In recent years some of the physiologic knowledge gained has resulted in the development of valuable physical measures for producing hypothermia as an adjunct to the anesthesia in cardiac surgery. Numerous discussions of this important use of hibernation are available in the literature.

"Artificial hibernation" produced by drugs as a therapeutic measure for medical conditions is something quite different. It relates chiefly to the use of chlorpromazine which was not discovered until 1950. Its use, moreover, is seemingly not only for the hypothermia it produces, but for its action in depressing the central and autonomic nervous systems—its action as a *neuroplégique* as the French term it. We are not referring to the use of chlorpromazine in small oral doses for conditions such as neuropsychiatric disorders. These were reviewed in the JOURNAL last February by Bakwin (**48**: 240, 1956).

Artificial hibernation, in which the hypothermia is brought about by chlorpromazine, is a rather drastic therapeutic measure in use in a number of European clinics, chiefly French we gather from the reports, for the treatment of children seriously ill with toxic conditions due to a number of causes. Perhaps it can best be described by briefly outlining the procedure as taken from a recent description. It varies somewhat in details as used in different clinics, but the general principle is the same.

The patient lies uncovered on the bed, which is slightly sloped to ensure adequate blood supply to the brain. The hibernation fluid is then infused. This contains Largactyl (the European trade name for chlorpromazine) in strength to make 1 mg. per milliliter. To this is added antibiotics and, by some, such drugs as Phenergan and Dolosol. A dose of

1 mg. per kilogram of body weight is administered, divided into three or four doses at intervals of twenty to thirty minutes, until "hibernation equilibrium" is reached. By this is meant that the patient becomes quiet and somnolent, the body temperature is lowered, and the respirations steady and regular. In mild cases the chlorpromazine is given at times by mouth. If the temperature does not fall rapidly some add ice packs. The treatment has been used for many severe toxic conditions such as the meningitides, pneumonia, tetanus, toxic enteric conditions, paralytic poliomyelitis, etc.

In attempting to find out something about artificial hibernation, it was discussed last summer with a number of prominent European pediatricians from several different countries. We did not happen to meet a single one who looked favorably on the procedure from a practical or theoretical standpoint. Perhaps their feeling was well expressed by the reference to it as the "lytic cocktail," which apparently is an expression in common use in referring to the procedure. The favorable reports of its value we have read are based on post hoc arguments and conclusions. We feel its value is yet to be proved, and that clinics should be very slow and cautious in taking up this particular current vogue of therapeutic procedure.

"DISEASES OF MEDICAL PROGRESS"

UNDER this rather catchy title, Moser, in a recent issue of the *New England Journal of Medicine* (Sept. 27, 1956, p. 606), has collected a large number of "diseases that would not have occurred if sound therapeutic procedures had not been employed." One might quarrel with the word "sound" in some instances. As the author states in his conclusions, "Progress in every sphere of human endeavor creates new problems at each turn." The sum total resulting from "medical progress," however, as Moser presents them in this way, is rather appalling. Fortunately, in many, not all, of the therapeutic induced diseases the symptom complexes which develop disappear on withdrawal of the drug. Unfortunately some of the induced diseases end fatally, and others leave permanent disability.

The author lists over thirty conditions involving a number of systems. We quote a few examples: Collagen and Collagenlike Diseases, e.g., periarteritis nodosa; Neurological Diseases, e.g., Parkinsonism and psychoses; Hepatic Diseases, e.g., jaundice from intrahepatic obstruction; Hematologic Diseases, e.g., the not infrequent agranulocytic reaction induced by a number of drugs, and the anemias following certain specific surgical operations; Metabolic Diseases, e.g., retrolental fibroplasia; Cardiac Diseases, e.g., arrythmias; Renal Diseases, e.g., drug-induced nephroses; Dermatitides—these are legion. In addition, the author discusses fairly extensively the antibiotic-induced diseases and those induced by the steroids.

It is an interesting and provoking review.